APR 17 1939

VOLUME LXIV

NUMBER 4

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL

SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

April, 1939

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

Made in United States of America

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BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

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All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore, Md.

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Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

ANNOUNCEMENT

THE JOHNS HOPKINS HOSPITAL

FIFTIETH ANNIVERSARY CELEBRATION

May 4, 5 & 6, 1939

PROGRAM

May 4

Morning—Registration; Scientific Programs, Clinics and Demonstrations.
1 P.M.—Luncheon.
3 P.M.—Public Meeting at Hospital.

ORDER OF EXERCISES

Invocation

Welcome

HON. HENRY D. HARLAN, President, Board of Trustees, The Johns Hopkins Hospital.

Greetings

DR. IRWIN ABEL, President, American Medical Association.
DR. HOWARD NAFFSIGER, President, American College of Surgeons.
DR. FRED CARTER, President, American Hospital Association.
DR. O. H. PERRY PEPPER, President, American College of Physicians.
MAJOR JULIA C. STIMSON, President, American Nurses' Association.

Address

DR. JAMES B. HERRICK, Emeritus Professor of Medicine, Rush Medical College of Chicago.

8:30 P.M.—Play Dealing with Early History and Development of Hospital—probably given in Eastern High School Auditorium.

May 5

Morning—Scientific Programs, Clinics and Demonstrations.
1 P.M.—Luncheon.
3 P.M.—Commencement for School of Nursing.

ORDER OF EXERCISES

Invocation

Greetings

MISS EFFIE TAYLOR, Dean, School of Nursing, Yale University; President, International Council of Nurses.

MISS ISABEL STEWART, Director, Department of Nursing and Health, Teachers College, Columbia University.

MISS NELLIE X. HAWKINSON, Professor, Nursing Education, University of Chicago; President, National League of Nursing Education.

Address

MISS ELSIE M. LAWLER, Principal, School of Nursing, The Johns Hopkins Hospital.

Awarding of Scholarships

HON. HENRY D. HARLAN, President, Board of Trustees, The Johns Hopkins Hospital.

Presentation of Diplomas

DR. WINFORD H. SMITH, Director, The Johns Hopkins Hospital.

7:30 P.M.—Banquet, Emerson Hotel. For Doctors, Nurses, Trustees and Guests.

May 6

Morning—Scientific Programs, Clinics and Demonstrations.

1 P.M.—Luncheon.

2:30 P.M.—Hospital Moving Pictures.

(*Note:* The morning programs have not yet been completed. On each of the three mornings there will be a general scientific session, and, in addition, clinics, operations and demonstrations in the various departments of the hospital. The papers at the scientific sessions will be contributed largely by former members of the hospital staff who are returning for the celebration.)

MACROCYTIC ANEMIA IN ASSOCIATION WITH INTESTINAL STRICTURES AND ANASTOMOSES

Review of the Literature and Report of Two New Cases

W. HALSEY BARKER, M.D., AND L. EDGAR HUMMEL, M.D.*

From the Hospital of the Rockefeller Institute for Medical Research

Submitted for publication January 2, 1939

The clinical picture of pernicious anemia in conjunction with intestinal strictures or anastomoses has been the subject of a number of reports since Faber first called attention to such an association in 1895. Reviews of the subject by Meulengracht in 1929 and Hurst in 1933 brought the number of recorded cases up to 30. We have collected 19 more cases from the literature to which we can add two of our own, thus raising the total number of cases to 51. The brilliant response of certain of the reported cases to surgical correction of the intestinal abnormality has furnished convincing evidence that the association between the intestinal lesion and the anemia is more than a coincidental one. However, considerable difference of opinion exists on two points: 1) the mechanism of the production of the anemia, and 2) the most effective form of therapy. It is our purpose to discuss these questions in the light of our own experience with two cases of macrocytic anemia occurring in patients with intestinal anastomoses and with the aid of information gathered in an analysis of the cases reported in the literature.

REPORT OF CASES

Case 49. D. S., male, aged 56, dentist.

History: The patient was admitted to the Hospital of The Rockefeller Institute on December 28th, 1935 with a complaint of weakness and diarrhea. He had enjoyed fairly good health until five years before. He had had the usual childhood diseases but no other serious infections except for right-sided pleurisy with effusion

* Dr. Barker is now Instructor in Medicine, The Johns Hopkins School of Medicine; Dr. Hummel is Assistant in Medicine, University of Buffalo Medical School.

in 1917. He spent 6 weeks in bed at this time and did not work for 2 years. Tubercle bacilli were never found in his sputum.

The patient's digestion was always rather easily upset and since youth he had suffered 8 to 10 attacks every year which were marked by abdominal pain, vomiting and diarrhea, lasting 2 to 3 days. Between such attacks he was subject to mild constipation. In the fall of 1930 his indigestion became worse, and he suffered with epigastric fullness, belching, and heart-burn after practically every meal. Various medicines were tried without effect. In February, 1931 a laparotomy was performed and a fecalith was removed from the ileum. The lower ileum was found to be thickened and indurated. The patient's blood count was normal at this time. He experienced some relief following the operation, but in the spring of 1932 the abdominal complaints again became severe and the constipation became more marked. In June 1932, 18 inches of the lower ileum were resected. The pathological diagnosis was non-specific ileitis. He recovered slowly from this second operation but was eventually able to return to work. In June 1934, 2 years later, he was forced to stop work because of weakness. A mild macrocytic anemia was noted at this time, which did not respond appreciably to weekly injections of liver extract or to iron by mouth. In November 1934 a diagnosis of partial intestinal obstruction was made, and the patient was operated on at the Mayo Clinic, where an anastomosis between the lower ileum and the transverse colon was performed. There was well marked macrocytic anemia before the operation, which failed to respond to parenteral liver extract. The red blood cell count rose rapidly after the operation and he was discharged with a mild hypochromic microcytic anemia. However, he soon developed diarrhea with three to six yellow foamy stools a day, which persisted up to the time of his admission to this hospital. There was marked flatulence and gaseous distention. The rectum was often quite sore, and occasionally he experienced burning of the tongue. He developed increasing weakness and pallor. There had been a loss of 40 pounds in weight over the 5 year period of his illness, although his diet had been excellent.

Physical Examination: The patient was a pale, emaciated, white man who was not acutely ill. Weight 45.7 kg. There was slight edema of the feet. The tongue and buccal mucosa appeared normal. There was evidence of thickened pleura and chronic bronchitis over the lower right lung. The heart and blood pressure were normal. The abdomen was distended and boggy. There were numerous operative scars and diastasis recti. Intestinal patterns were readily visible. There was no abdominal tenderness and no abnormal masses were felt, although there was some resistance and fullness in the right lower quadrant. Neurological examination was quite normal except for questionable slight diminution in vibratory sensation in the feet.

Laboratory Findings: Blood count showed—R. B. C. 2,350,000, hemoglobin 69%, W. B. C. 3,800, M. C. V. 124 μ^3, C. I. 1.47, icteric index 3, reticulocytes 2%. Differential was normal except for 6% eosinophils. Platelets 520,000. The smear showed definite anisocytosis with a preponderance of hyperchromic macro-

cytes; little poikilocytosis. *Urine* was normal. The *stools* were liquid, gray-brown in color, with occult blood on occasions; excess fat was present. *Gastric analysis:* No free hydrochloric acid in the fasting specimen, but abundant free acid after alcohol test meal, and a rise to 87° after histamine. *Sternal marrow biopsy* revealed a red, highly active marrow (Figs. 3A and 4A). Supra vital differential count (500 cells) showed:

	per cent
Polymorphonuclears	28.7
Myelocytes (chiefly C)	15.1
Eosinophils	5.0
Normoblasts	18.0
Late Erythroblasts	14.7
Early Erythroblasts	9.5
Megaloblasts	2.5
Primitive Cells	6.5

Sections of the marrow showed marked erythro-megaloblastic hyperplasia such as is seen in the marrow of cases of pernicious anemia in relapse.

Liver Function: (1) Bilirubin excretion test: Patient given 50 mg. bilirubin intravenously. No retention after four hours. (2) 24 hour urine urobilinogen excretion 0.247 mg., a normal value. (3) Sodium benzoate test of Quick: 1.8 Gm. benzoic acid excreted in 4 hours, an abnormally low value suggesting liver damage or possibly poor absorption.

X-rays of gastro-intestinal tract revealed a normal stomach and showed the anastomosis between the ileum and transverse colon to be functioning well. The blind loop, consisting of the proximal part of the transverse colon, the ascending colon and the terminal ileum (Fig. 1), filled by retrograde flow of the barium. The terminal ileum was obviously diseased, with several large lakes of barium separated by narrow strictures.

Course: It was apparent that the patient was suffering from a sprue-like condition, with a well marked macrocytic anemia, and the question arose as to whether the deficient absorption of hematopoietic material or the absorption of toxic substances from the blind loop might be responsible for the anemia. A number of tests of intestinal absorption were carried out: 1) The potassium iodide test of Heath and Fullerton gave an appearance time of ten minutes for iodine in the saliva, a rapid normal value. 2) Glucose tolerance test showed a rise in blood sugar from 95 to 221 mg. per 100 cc. at the end of one hour with a slightly delayed fall.

The patient was given 1.25 Gm. of glucose per kilogram by mouth and the following figures for blood sugar were obtained:

Specimen	*Blood Sugar*
Fasting	95 mg. per 100 cc.
½ hour after glucose	211 mg. per 100 cc.
1 hour after glucose	221 mg. per 100 cc.
2 hours after glucose	139 mg. per 100 cc.
3 hours after glucose	139 mg. per 100 cc.

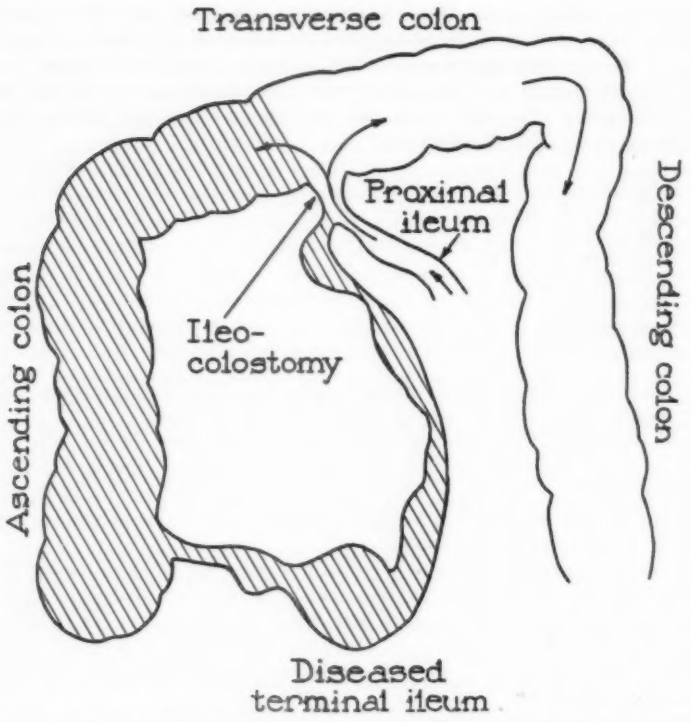

FIG. 1. *Case no. 49. Diagrammatic representation of the ileocolostomy.* The shaded area represents the short-circuited loop of bowel; the arrows show the course followed by the intestinal contents.

3) Fat absorption following a fat meal furnishing 4 grams of fat per kilogram of body weight showed 34% increase in the total plasma lipids after 4 hours. The figures obtained in the test were as follows:

Specimen	*Total plasma lipid carbon*
Fasting	403 mg. per 100 cc.
2 hours after fat meal	465 mg. per 100 cc.
4 hours after fat meal	539 mg. per 100 cc.
6 hours after fat meal	454 mg. per 100 cc.

This result compares favorably with the absorption of fat in normal individuals (Barker and Rhoads). The ingestion of the meal caused no unusual gastro-in-

testinal disturbances. 4) Ascorbic acid absorption: The patient was placed upon a diet low in vitamin C, and the 24 hour urinary excretion of ascorbic acid was followed. We are indebted to Dr. Julius Sendroy for carrying out the determinations on the urine. On the low vitamin C diet alone the patient excreted between 35 and 45 mg. of ascorbic acid in 24 hours. The diet was then supplemented with 250 mg. of crystalline ascorbic acid a day; there was no rise in the amount excreted over a 7-day period. Oral administration was then discontinued and 250 mg. of ascorbic acid were given intravenously each day for the next 7 days. Urinary excretion rose to 175 mg. on the 4th day and remained at a level between 160 and 250 mg. a day for the remaining 3 days of the test period. These results suggested deficient absorption of the ascorbic acid, destruction of the vitamin in the intestinal tract, or an unusual degree of unsaturation on the part of the patient. The patient was very uncomfortable while taking the vitamin C-free diet for study of his ascorbic acid metabolism. The erythrocyte count fell to 1,650,000 and the hemoglobin to 55% during this period, and his tongue became red and sore. The patient's reticulocytes were followed daily and on February 2nd he was given a diet for sprue, high in protein and low in carbohydrate and fat (Miller and Barker). Reticulocytes rose to 6.8% on the seventh day of this diet. Autolyzed yeast,[1] 15 Gm. a day, was then added and a second reticulocyte rise to 8.5% occurred. This reticulocyte rise during the administration of foods rich in Castle's extrinsic factor was regarded as evidence that the patient was secreting intrinsic factor in his stomach. Unfortunately it was impossible to test his gastric juice directly for intrinsic factor. The red blood cell count rose to 2,500,000 and the hemoglobin level to 70% on the regime of the diet for sprue and autolyzed yeast. When desiccated hog's stomach,[2] 20.0 Gm. a day, was added, the reticulocytes remained elevated between 4 and 8%, but there was no further rise in the erythrocyte count or hemoglobin. Finally the patient was given liver extract,[3] 12.0 Gm. a day by mouth (the amount derived from 300 Gm. of whole liver) and the reticulocytes once more showed a rise to 7.5%, after which they gradually dropped off to a level near 2%.

The patient was subjectively a good deal better while taking the liver extract by mouth, but mild diarrhea and flatulence persisted and the erythrocyte count did not rise above 3,500,000 with the hemoglobin level remaining at 70%. Therefore he was given liver extract parenterally, at first intravenously and later intramuscularly. There was a striking improvement in the gastro-intestinal symptoms and a further rise in the blood count during the period of parenteral liver extract administration. The course of the blood changes is depicted in figure 2. The patient was discharged from the hospital on May 8th, 1936. At the time he was feeling very well, with practically no diarrhea and very little flatulence. He had

[1] The preparation used was Vegex.

[2] The preparation used was Ventriculin.

[3] The preparation used was Liver Extract, Lilly, N. N. R.

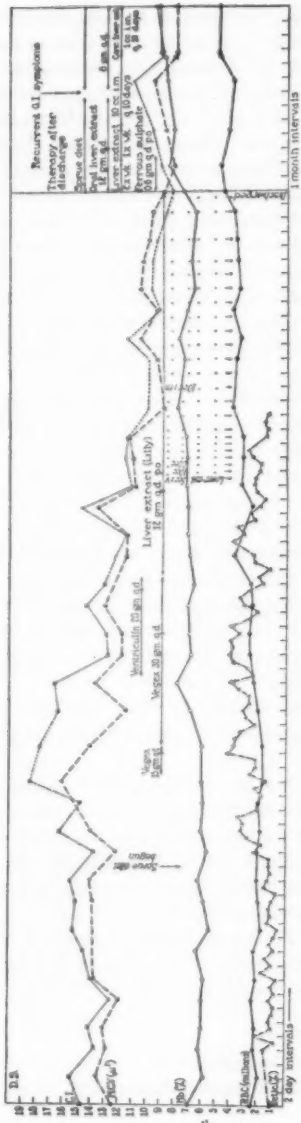

FIG. 2. *Case no. 49. Course of the blood under various forms of therapy.* On the scale, the values for Hb. (hemoglobin in percentage of normal) and M. C. V. (mean corpuscular volume) have been divided by 10, and the values for C. I. (color index) have been multiplied by 10.

gained 6.0 Kg. in weight during his stay in the hospital. At the time of discharge his red count was 4,550,000, hemoglobin 75%, and white count 7,900. Mean corpuscular volume and color index were both slightly lower than normal. For this reason small amounts of iron were added to his therapy.

He was sent home on the following regime:

(1) Sprue diet.
(2) Liver extract, three teaspoonfuls a day.
(3) Ferrous sulphate 0.2 Gm. three times a day.
(4) Intramuscular injection of 10.0 cc. liver extract, (the amount derived from 50.0 Gm. whole liver) twice a week.

Course following discharge from the hospital: Following discharge from the hospital the patient adhered closely to his therapeutic regime and continued to do very well. He was up and about the entire day. Gastro-intestinal symptoms did not recur. In September 1936 his blood count was as follows: R. B. C. 4,220,000, Hgb. 82%, W. B. C. 6,150, M. C. V. 88μ^3, C. I. 0.97. The interval between the liver extract injections was gradually lengthened to ten days. Toward the end of November he felt so well that he decided to abandon his diet and the oral liver extract, believing that the intramuscular injections would suffice to keep him symptom-free. Within a week of discontinuing the oral therapy, he developed abdominal cramps, diarrhea, and flatulence. These symptoms became so troublesome that he returned to the sprue diet and oral liver extract of his own accord. On December 21st, 1936, his blood picture once more showed a tendency to macrocytosis and hyperchromia, evidently associated with the flare-up of gastro-intestinal symptoms: R. B. C. 3,950,000, Hgb. 87%, W. B. C. 7,700, M. C. V. 95μ^3, C. I. 1.10. The gastro-intestinal symptoms cleared up within several weeks of this time. On February 15, 1937, he was readmitted to the hospital for further observation.

Physical Examination: The patient appeared vigorous and cheerful. Nutrition good, weight 52.8 Kg., no pallor or jaundice. Tongue normal. Bronchitic râles over the right lower lobe. Abdomen flat, soft, non-tender. Movable mass in the right lower quadrant suggesting a fecalith in the cecum or terminal ileum. Neurological examination normal.

Laboratory Findings: Blood count: R. B. C. 4,880,000, hemoglobin 88%, W. B. C. 7,000 with normal differential. M. C. V. 81μ^3, C. I. 0.90, icteric index 5, reticulocytes 0.4%. Smear: Red cells appear normal; platelets abundant. *Urine:* Negative. *Stool:* Semi-formed; no gross blood; guaiac +. *Barium Enema:* Appearance of colon and ileum identical with that of a year before. Ileo-colostomy patent and functioning well.

Liver Function: 1) Serum bilirubin 0.3 mg. per 100 cc. 2) Bilirubin liver function test: No retention after 4 hours. 3) Sodium benzoate liver function test: 3.453 Gm. benzoic acid excreted in 4 hours, a normal result in contrast to the very low output at the time of his first admission.

Sternal Marrow Biopsy: Specimen of marrow appeared quite cellular in the gross, with few spicules of bone. The supravital differential count (500 cells):

	per cent
PMN	50.0
Myelocytes B	0.2
Myelocytes C	18.8
Basophils	0.6
Eosinophils	4.8
Normoblasts	20.0
Late Erythroblasts	2.4
Early Erythroblasts	0.2
Primitive Cells	2.4

Sections of the marrow (Figs. 3B and 4B) presented an essentially normal picture. There was considerable fat present; no megaloblasts were seen in contrast to the striking megaloblastic hyperplasia noted at the time of the previous biopsy.

Course: The patient was discharged 5 days after admission to continue on the same therapeutic regime with the exception that a more concentrated liver extract preparation was to be substituted for the dilute extract previously used. In the spring of 1938, two years after his first admission, he again complained of mild gastro-intestinal symptoms. Since for economic reasons he had cut down the amount of liver extract he was taking, it seemed likely that this most recent recurrence of symptoms was due to inadequate therapy. When last heard from, he was once more symptom-free.

Summary: A 56 year old white man had suffered from symptoms of partial intestinal obstruction due to non-specific ileitis for 4 years. Shortly after an ileocolostomy was performed for relief of the obstruction, the patient developed a severe macrocytic anemia, associated with diarrhea, flatulence, glossitis, and loss of weight. The chief physical findings were pallor, emaciation and abdominal distention. There were no neurological changes. The blood picture was that of a severe macrocytic anemia with leucopenia. There was no increase in serum bilirubin or urobilinuria. The bone marrow showed megaloblastic hyperplasia. The absorption of glucose, fat, and iodide from the intestine was normal. Gastric acidity was normal after a test meal. Indirect evidence for the presence of the intrinsic factor in the gastric juice was furnished by the fact that the reticulocytes rose and the blood levels improved on a diet rich in Castle's extrinsic factor. However, complete alleviation of the gastro-intestinal symptoms and disappearance of the anemia only occurred after the dietary regime had been supplemented with intensive parenteral liver extract therapy. Except for mild relapses of gastro-intestinal symptoms when he has broken away from his therapeutic regime, the patient has remained clinically well, with a normal blood picture for two years following discharge from the hospital.

Case 50. R. J., male, aged 35, waiter.

History: This patient was admitted to the Hospital of The Rockefeller Institute

on February 4, 1937, complaining of abdominal cramps, loss of weight, and weakness. He had enjoyed good health until 1922 when he began to suffer from epigastric pain, coming on 1–2 hours after meals and relieved by soda. After a short period of hospital treatment he was much improved and remained asymptomatic until 1930 when he suddenly awoke with excruciating abdominal pain. He was taken to the Bellevue Hospital where an emergency operation was performed for a perforated peptic ulcer; a gastro-jejunostomy was done at the time. Following this operation he still had mild epigastric distress and was troubled with abdominal distention and borborygmi. Eighteen months later he suddenly had a gross hematemesis. He was again admitted to the Bellevue Hospital and given a strict diet. X-rays revealed no definite ulceration. He then remained fairly well for 2 years before he suffered a second hematemesis. On this occasion he was admitted to another hospital where x-rays were interpreted as showing a duodenal ulcer. Coincident with this hematemesis the patient began belching very foul gas having a fecal odor. At operation no ulcer was found but abdominal adhesions were broken up. Following the operation the patient was worse with marked borborygmi, flatulence, diarrhea, anorexia, and loss of strength and weight. At times his stools would contain food which he had eaten only 2–3 hours before. Because red meat did not agree with him, he eliminated this from his diet. However, he continued to take a fairly well balanced diet with broiled liver at least 4 times a week in addition to fresh vegetables and fruit. Between periods of anorexia, his appetite was at times voracious, yet he steadily lost weight. On one occasion gas that he eructated while lighting a cigarette caught fire and singed his mustache. After this episode he kept his face clean-shaven.

The patient lost ground slowly over the next 18 months until December, 1936, when he was forced to stop work. Two weeks before admission to the Rockefeller Hospital the diarrhea gave way to constipation and the eructation of gas decreased. Although pallor was never marked, a definite macrocytic anemia was noted at the New York Hospital and it was for further study of this anemia that the patient was transferred to the Rockefeller Hospital. He had at no time suffered from sore tongue or neurologic symptoms.

Physical Examination: The patient was a small, emaciated, moderately pale man who had obviously lost much weight. The skin was slightly atrophic and drawn tight over the bony eminences of the body. The conjunctivae were somewhat pale; the sclerae were clear with no suggestion of icterus. The teeth were in fair shape; the oral mucosa and tongue appeared normal. There was no enlargement of the lymph nodes. The thyroid was not enlarged. The heart and lungs were normal. Blood pressure 115/80. The abdomen was rounded and distended with gas; it was extremely tympanitic. Scars from previous operations were in evidence. There was definite tenderness over the mid-epigastrium, more marked on rebound, and an increased resistance to palpation over the right side of the abdomen. The edge of the liver, sharp, smooth, and slightly tender, was palpable 2 to 3 cm. below the right costal margin; no other viscera or masses were felt. There was slight tenderness on rectal examination. Definite clubbing of the

fingers and toes and slight acrocyanosis were noted. Neurologic examination was normal.

Laboratory Findings: Blood Count: R. B. C. 3,620,000, Hgb. 100%, W. B. C. 4,400 with normal differential count. M. C. V. 119μ^3, C. I. 1.38, icterus index 3. Platelets 310,000. The blood smear showed a striking uniformity in the size of the erythrocytes with a distinct tendency to macrocytosis but little poikilocytosis.

Urine: Normal.

Stools: Pale, yellow with many fat globules, fatty acid crystals, and starch granules; no parasites or ova; guaiac test negative.

Gastric Analysis: Showed a large amount of material in the fasting stomach, yellowish-gray in appearance, with a mixed yeasty and fecal odor. This material contained some free HCl. No typical gastric juice was obtained. A subsequent gastric analysis several weeks later showed typical fasting contents with free HCl of 65°.

Liver Function Tests: 1) Bilirubin excretion test:—Original plasma bilirubin level 0.6 mg. per 100 cc.; no retention of injected bilirubin after 4 hours. 2) Sodium benzoate test (2 separate occasions):—2.969 Gm. of benzoic acid and 2.58 Gm. benzoic acid excreted in 4 hours, slightly subnormal values. 3) Galactose tolerance test: trace of galactose excreted during the 4-hour period, a normal result.

Tests of intestinal absorption: 1) Glucose tolerance test: The patient was given 54.0 Gm. glucose by mouth (1.25 Gm. per Kg. body weight); the blood sugar rose from fasting level of 70 mg. to 125 mg. per 100 cc. at the end of one hour, pointing to fairly good absorption of glucose from the intestine. The actual figures for the test were as follows:

Specimen	*Blood Sugar*
Fasting	70 mg. per 100 cc.
½ hour after glucose	112 mg. per 100 cc.
1 hour after glucose	125 mg. per 100 cc.
2 hours after glucose	75 mg. per 100 cc.
3 hours after glucose	55 mg. per 100 cc.
4 hours after glucose	53 mg. per 100 cc.

2) Fat absorption test: After the ingestion of a fat meal furnishing 2 Gm. fat per kilo body weight, the patient showed a delayed but fairly good rise in the blood fat level:

Specimen	*Total plasma lipid carbon*
Fasting	250 mg. per 100 cc.
2 hours after fat meal	257 mg. per 100 cc.
4 hours after fat meal	448 mg. per 100 cc.
6 hours afterfat meal	258 mg. per 100 cc.

3) Ascorbic acid absorption test: The patient showed a good response to the oral administration of 250 mg. ascorbic acid a day as measured by the increase in the 24 hour urinary output of ascorbic acid.

Fluoroscopy and X-rays of the gastro-intestinal tract showed a normal esophagus. The stomach was long and filled in its lower portion; when the barium reached a certain level, it appeared to spill out through a stoma into the jejunum. After considerable barium had passed into the small intestine, there appeared to be some spilling of barium into the colon although the point of communication could not be made out. X-rays confirmed the fluoroscopic findings and also showed some barium passing through the pylorus into the duodenum. A barium enema revealed a redundant relaxed colon which filled slowly; the barium did not pass beyond the middle of the transverse colon until pressure was exerted over the abdomen. Then the barium appeared to pass both into the rest of the colon and into the stomach. Previous x-rays taken at the New York Hospital had definitely established the presence of a gastro-jejuno-colic fistula.

Course: 1) After the diagnostic studies had been completed, the patient was given a diet for sprue, supplemented with autolyzed yeast, 12 Gm. a day. There was no definite improvement on this regime. 2) Therapy was changed from autolyzed yeast to liver extract, 12 Gm. a day (the amount of extract derived from 300 Gm. whole liver). The patient became more uncomfortable with abdominal distention and pain so that after a short trial the diet and liver extract had to be abandoned. His blood showed no change. It was felt at this time that a recurrence of the gastric ulcer or a jejunal ulcer might be responsible for some of his symptoms. 3) He was therefore placed upon the Meulengracht diet for bleeding ulcer (Meulengracht, 1936) with alkaline powders, and intravenous injections of liver extract were started. On this regime he had less abdominal discomfort but passed 3–4 loose stools a day and his blood count failed to improve materially. 4) Previous therapy was discontinued and the sprue diet resumed; the patient was also given intramuscular injections of calcium gluconate. Abdominal discomfort persisted until desiccated hog stomach, 20 Gm. a day, was started. This addition appeared to relieve the abdominal discomfort and to regulate the bowels. However, his blood count fell until the R. B. C. reached 2,980,000 and Hgb. 70%. Intramuscular injections of concentrated liver extract[4] (1 cc. derived from 100 Gm. whole liver) were then given and the patient was discharged from the hospital on August 5, 1937 to return to the out-patient clinic twice weekly for further injections of liver extract and calcium gluconate. He followed the diet for sprue as well as he could at home. Although he continued to have gaseous distention, foul eructations, and mild diarrhea, his general condition and blood count showed distinct improvement.

September 14: Wgt. 44.4 Kg., a gain of 8.0 Kg. from the lowest point during his hospital stay. R. B. C. 3,830,000, Hgb. 83%, M. C. V. 103μ^3, C. I. 1.09.

October 18: Wgt. 45.5 Kg. November 29: Diarrhea had increased; weight 42.1 Kg.

Because of the persistence of the gastro-intestinal symptoms and the recent loss of weight, the patient was admitted to the New York Hospital on December 1 for

[4] The preparation used was Concentrated Liver Extract, Lederle.

TABLE I

CASE NO.	AUTHOR	YEAR	SEX	AGE	GLOSSITIS	G-I SYMPTOMS	ICTERUS	R. B. C.	HGB	C. I.	MACROCYTOSIS	FREE HCl*	INTESTINAL LESION	TREATMENT	RESULT†
								millions	*per cent*						
1	Wallis and Warfvinge	1893	F	73		+	+	1.40	40	1.43	+	0[m]	4 non-tbc. strictures in lower jejunum and ileum		Died, autopsy
2	Faber	1895	F	27		+		0.60	20	1.66	+		2 non-tbc. strictures of jejunum		Died, autopsy
3	Holst	1896	F	49		+	+	0.48	20	2.08	+		14 non-tbc. strictures of ileum		Died, autopsy
4	Borchegrevink	1898	M	59		+		Severe anemia					4 tbc. intestinal strictures	Milk diet	Temp. improved; died, autopsy
5	Barker and Hunter	1900	M	28		+		1.00	20	1.00	+	+[v]	Traumatic stricture of jejunum		Died, autopsy
6	Gluzinski	1911	F	44		+	+	1.12	31	1.39	+	0[m]	Multiple constricting tbc. ulcers of jejunum and ileum		Died, autopsy
7	Bretschneider	1911	M	27		+		0.89			+		Multiple tbc. strictures of small intestine		Died, autopsy
8	A. Schmidt	1914	?					Severe pernicious anemia					Stricture of small intestine		Died, autopsy
9	A. Schmidt	1914	?					Severe pernicious anemia					Stricture of small intestine		Died, autopsy
10	Meulengracht	1921	F	38		+	+	2.70	50	0.93	+	0[m]	Fibrous stricture in upper colon		Died, autopsy
11	Meulengracht	1921	F	56	+	+	+	1.70	39	1.15	+	0[m]	Fibrous stricture of lower ileum	Arsenic and kefir milk	Temp. improved; died, autopsy
12	Meulengracht	1922	F	64		+	0	1.34	40	1.50	+	0[m]	3 tbc. strictures of small intestine	Operation	Died, autopsy (V)
13	Szczepanski	1923	F	40				Typical pernicious anemia					Tbc. mesenteric adenitis and intestinal strictures		Died, autopsy
14	Meulengracht	1922 1929	M	52	+	+	+	1.46	45	1.52	+	0[m]	Operative anastomosis and p-o strictures	(a) arsenic and kefir milk (b) liver therapy	Remissions and relapses Cure (VI)
15	Seyderhelm	1924 1927	F	?				Pernicious anemia					Stricture of small intestine	Operation	Cure (V)
16	Kretz	1925	F	27	+	+		3.73	78	1.04	+		Tbc. stricture of cecum		Died, autopsy

17	Wiechmann and Zinsser	1926	F	22	+	+		0.95	26	1.37	+	0[m]	Stricture of ascending colon		Died
18	Zadek	1926	F	44	+	0	+	0.81	19	1.17	+	0	Tbc. ulcer and stricture of lower ileum		Died, autopsy
19	Zadek	1926	M	65	0	0	0	3.64	79	1.06	0	0	Fibrous tbc. ulcer of transverse colon		Died, autopsy
20	Deutsch	1926	F	13		+	+	1.75	40	1.14	+	+[m]	Small intestine constricted by tbc. adhesions (x-ray)	Carbohydrate and milk diet	Improved
21	W. Schmidt	1927	M	71	+	+		0.88	28	1.75	+	0	Adhesions constricting descending colon		Died, autopsy
22	Hartmann	1929	F	67		+		2.26	50	1.13	+	0[m]	Foreign body in abdominal cavity with intestinal anastomosis and blind cul-de-sac		Died, autopsy
23	Meulengracht	1929	F	63	+	+		2.60	60	1.17	+	0[m]	3 strictures of lower ileum; prob. tbc.	Operation	Died, autopsy (V)
24	Little, Zerfas, and Trusler	1929	M	28	+	+	+	1.30			+	+[m]	2 operative entero-enterostomies and fecal fistulas	(a) Operation (b) Liver therapy	Improved (VII) Temp. improved. Later died, autopsy
25	Taylor	1930	F	54	+	+	+	1.20	42	1.75	+	0[b]	Multiple diverticula of intestine	(a) Liver therapy (b) Operation	Improved Died, autopsy (VII)
26	Becker	1930	F	65	+			1.87	48	1.28		+	Ca. of hepatic flexure with stricture	Liver therapy	Died, autopsy (VI)
27	de Rivas	1930	M	55		+		Sprue anemia					Gastro-colostomy		Died, autopsy
28	Scherer	1930	F	44	+	+	+	2.04	44	1.08	+	0[m]	Tbc. stricture of lower ileum	Operation	Improved (V)
29	Strandell	1931	F	56		+		0.90	30	1.69	+	0[m]	Multiple strictures of ileum		Died, autopsy
30	Strandell	1931	F	48	+	+	+	1.70	48	1.41	+		Adhesions constricting transverse colon		Died, autopsy
31	Castle, Heath and Strauss	1931	M	41	+	+	+	0.91	35	1.90	+	+[b]	Muitiple operative anastomoses and p-o fistulae	Liver therapy	Improved (VI)
32	Narbeshuber	1931	F	30	+	+	+	2.16	50	1.16	+	+[m]	Entero-enterostomy and ileocolostomy to circumvent 3 tbc. strictures	Liver therapy	Cure (VI)
33	Fairley and Kilner	1931	M	42	+	+	0	3.60	65	0.90	+	+[f]	Gastro-jejuno-colic fistula	(a) Liver therapy (b) Operation	Improved Cure (VII)
34	Fairley and Kilner	1931	M	49	+	+	0	3.13	77	1.22	+	+[f]	Ca. of stomach; gastro-jejuno-colic fistula	(a) Liver therapy (b) Operation	Improved Died (VII)
35	Fairley and Kilner	1931	M	58	+	+	0	3.60	68	0.94	+		Gastro-jejuno-colic fistula	Liver therapy	Died, autopsy (VI)

TABLE I—*Concluded*

CASE NO.	AUTHOR	YEAR	SEX	AGE	GLOSSITIS	G- SYMPTOMS	ICTERUS	R. B. C.	HGB	C. I.	MACROCYTOSIS	FREE HCl*	INTESTINAL LESION	TREATMENT	RESULT†
								millions	*per cent*						
36	Bremer	1932	?					Pernicious anemia					Strictures of small intestine		Died, autopsy
37	Bremer	1932	?					Pernicious anemia					Strictures of small intestine		Died, autopsy
38	Hurst	1933	F	30	+	+	+	2.20	54	1.23	+	+	P-o strictures and operative anastomoses	Operation	Died (V)
39	Emile-Weil, Stieffel, and Bousser	1933	M	65	0	+	+	1.10	40	1.82	+	+[h]	Adhesions obstructing ascending and trans. colon	Liver therapy	Died, autopsy (VI)
40	Schlesinger	1933	F	54	+	+	+	1.53	37	1.21	+	+[m]	Operative entero-enterostomy; some obstruction	Liver therapy	Improved (VI)
41	Strauss Castle	1934 1937	M	8	+	+		1.27	24	0.95	+	+	2 operative entero-enterostomies	Liver therapy	Cure (VI)
42	Christopher	1935	M	17		+		1.89	45	1.19			Operative jejuno-colostomy and obstructed ileo-colostomy	Operation	Cure (V)
43	Sturgis	1936	F	42	+	+	0	2.97	65	1.09	+	+[h]	Ileo-colostomy with long loop	Liver therapy	Cure (VI)
44	Hawksley and Meulengracht	1936	F	49	+	+	0	1.96	45	1.15	+	0[m]	Active tbc. with multiple strictures	(a) Liver therapy (b) Operation	Slightly improved Died, autopsy (VII)
45	Minot Richardson	1936 1938	M	30	+	+	+	2.90	60	1.04	+	+[m]	Entero-enterostomy short-circuiting nearly ½ small intestine	(a) Liver therapy (b) Operation	Improved Cure (VII)
46	Butt and Watkins	1936	F	49		+		3.19	88	1.37	+	0	Subacute ileitis and colitis with some obstruction	Operation	Cure (V)
47	Butt and Watkins	1936	M	55		+		2.93	81	1.38	+	0	Ileitis and colitis with obstruction	(a) Liver therapy (b) Operation	Improved Died, autopsy (VII)
48	Butt and Watkins	1936	F	60	+	+		3.25	89	1.37	+	0	Multiple fecal fistulae	Operation	Died (V)
49	Butt and Watkins	1936a	M	55		+		3.59	84	1.16	+	+	Chronic ileitis with partial obstruction	(a) Operation	Temp. improved; relapse (VII)
	Barker and Hummel	1938b			+	+	0	2.35	69	1.47	+	+[m]	Operative ileo-colostomy	(b) Liver therapy	Cure
50	Barker and Hummel	1938	M	35	0	+	0	3.62	100	1.38	+	+[f]	Gastro-jejuno-colic fistula	(a) Liver therapy (b) Operation	Temp. improved Died, autopsy (VII)
51	Bethell	1938	M	29	0	+	+	2.48	60	1.20	+	+[h]	4 strictures of lower ileum	(a) Liver therapy (b) Vegex therapy (c) Operation	Slightly improved Much improved (VII) Temporary cure

* The letters after the symbols + or 0 may be interpreted as follows: "f" = fasting; "m" = after test meal; "h" = after histamine; "v" = vomitus.
† The Roman numerals V, VI, VII after certain cases refer to Tables V, VI, VII in which the therapy and result are given in more detail.

operative correction of the gastro-jejuno-colic fistula. At this time his blood picture was as follows: R. B. C. 3,700,000, Hgb. 85%, W. B. C. 9,000. On December 8 the gastro-jejuno-colic fistula was repaired and the normal continuity of the gastro-intestinal tract was restored. Following the operation patient did well at first, but still complained of epigastric pain from time to time. On January 18, 1938 his stools became tarry and the red blood cell count had dropped to 2,700,000. Gastric lavage and x-rays showed considerable gastric retention. The patient was then given several transfusions and the abdomen was explored on February 15. Since the original ulcer was found to be perforating into the pancreas, a gastric resection by the Polya technique was carried out but the patient developed a duodenal fistula, generalized peritonitis and bronchopneumonia of which he died on February 24, 9 days after the second operation.

Autopsy[5] revealed unhealed wounds of resection of the pylorus with gastro-enterostomy and entero-enterostomy; a communication between the duodenum and the peritoneal cavity at the point of closure of the duodenum; generalized peritonitis; an ulcer of the transverse colon at the site of closure of the jejuno-colic fistula; hydrothorax, left; extensive atelectasis of the lower lobes of both lungs; abscesses in the kidneys; petechiae and ecchymoses of the skin, pericardium, pleura, and mucosa of the stomach and bladder. The liver was normal to both gross and microscopic examination. The vertebral bone-marrow was grossly quite red and sections showed a moderate increase of cellularity with a very definite decrease in mature forms of both the white cell and the red cell series. There were practically no normoblasts and very few leucocytes or adult myelocytes present. Young myelocytes and crythroblasts were abundant in addition to a number of cells which were interpreted as megaloblasts.

Summary: A 35 year old white waiter had suffered from symptoms of a gastric ulcer since 1922. Eight years after the onset of symptoms the ulcer perforated. A gastro-enterostomy was performed at this time. During the next 4 years he suffered two large hematemeses and coincident with the second of these he developed fecal belching. In 1935 a second operation was performed for release of adhesions. Subsequently he developed anorexia, flatulence, and diarrhea, and there was progressive loss of strength and weight. The principal physical findings on admission to the hospital in 1936 were emaciation, slight pallor, gaseous abdominal distention, epigastric tenderness, slight enlargement of the liver, and clubbing of the fingers and toes. There were no neurologic abnormalities. A slight anemia, macrocytic in type, with leucopenia was noted. Free hydrochloric acid was present in the gastric juice. Roentgenographic study of the gastro-intestinal tract revealed a gastro-jejuno-colic fistula. The absorption of glucose, fat, and ascorbic acid from the intestinal tract was surprisingly good. Although the patient at first gained weight on a therapeutic regime consisting of a diet for

[5] We are indebted to Dr. William Andrus of the Cornell University Medical School for permission to include details of the patient's course at the New York Hospital and the results of the post-mortem examination.

* The letters after the symbols + or 0 may be interpreted as follows: "f" = fasting; "m" = after test meal; "h" = after histamine; "v" = vomitus.
† The Roman numerals V, VI, VII after certain cases refer to Tables V, VI, VII in which the therapy and result are given in more detail.

(c) Operation | Temporary cure

sprue and intramuscular injections of liver extract, the gastro-intestinal symptoms and the macrocytic anemia persisted. For these reasons an operation was performed and the gastro-jejuno-colic fistula was repaired. The patient improved temporarily but then developed pyloric obstruction and melena, necessitating a second operation two months later. Following this he died of peritonitis. At autopsy the bone marrow was found to be hyperplastic with immature cells of both the erythroid and the myeloid series predominating.

ANALYSIS OF 51 CASES

The principal clinical and pathologic features of 51 cases (49 from the literature and 2 of the authors) of macrocytic anemia associated

TABLE II

Symptomatology and laboratory data in 51 cases

	PRESENT	ABSENT	NOT MENTIONED
Gastro-intestinal symptoms	42	2	7
Glossitis	25	4	22
Icterus	18	10	23
C. N. S. involvement	10	12	29
Anemia	51		
Macrocytosis	39	1	11*
Hyperchromia	32	10	9
Leucopenia	30	6	15
Free HCl in gastric juice†	17	19	15

* Anemia spoken of simply as "pernicious anemia" in these cases; no specific mention of macrocytosis.

† See Table III for further analysis.

with intestinal stricture or anastomosis are presented in chronological order in Table I. The frequency with which certain symptoms, hematologic changes, and abnormalities of gastric secretion occurred are summarized in Table II.

INCIDENCE AND SYMPTOMATOLOGY

Age and Sex. The ages of the patients ranged from 8 years to 75 years in 46 cases; in the other 5 cases the age was not given. Thirteen of the 46 patients, or 28 per cent, were less than 30 years of age when they developed their anemia, and 3 of the patients were under 20. Thus the incidence of this form of anemia in young people is con-

siderably higher than is the case in a comparable series of patients with true "idiopathic" pernicious anemia.

The sex was specified in 47 cases, of which 27 were females and 20 males.

Gastro-Intestinal Symptoms. Disturbances referable to the gastro-intestinal tract were prominent in 42 of the 44 cases, where symptomatology was given. The symptoms were essentially those of partial intestinal obstruction: diarrhea or intermittent diarrhea and constipation, distention, abdominal cramps, and less frequently nausea and vomiting. Visible intestinal peristalsis and audible borborygmi were frequently noted along with abdominal fullness and tenderness, especially in the right lower quadrant. Fecal belching was a feature in the cases of gastro-jejuno-colic fistula. Marked loss of weight, secondary to the gastro-intestinal disturbances, was the rule.

Glossitis. Soreness of the tongue, with or without papillary atrophy, was present in 25 cases, absent in 4, and not mentioned in 22. The incidence of some form of glossitis in this form of anemia is comparable to that in true pernicious anemia and sprue.

Icterus. The presence or absence of icterus was mentioned in 28 cases; 18 of these showed clinical icterus, confirmed in many instances by a positive van den Bergh reaction or an elevated icterus index. In one case (no. 20) the level of the serum bilirubin was 6.0 mg. per 100 cc.; in another case (no. 45) the icterus index was 60.

Neurologic Symptoms. Symptoms and signs of involvement of the nervous system were not so common in this group of patients as in patients with true pernicious anemia. In only 4 cases (nos. 24, 25, 35 and 38) was objective evidence of disease of the nervous system described; 3 of these cases presented signs of combined degeneration of the spinal cord whereas one (no. 35) had a peripheral neuritis. Six other patients complained of paresthesias in the extremities, but showed no objective neurologic changes. In 12 cases there was said to be no involvement of the nervous system whatsoever; no mention of neurologic manifestations was made in the other 29 cases.

LABORATORY DATA

Blood Picture. Anemia of the pernicious type was present in all 51 cases. Actual figures for erythrocyte and hemoglobin levels

were given in 44 cases. The red blood cells varied from 480,000 to 3,730,000 per cubic millimeter; in 8 cases the erythrocyte count was below 1,000,000. The values for hemoglobin varied from 19 per cent to 100 per cent.

The occurrence of macrocytosis was mentioned specifically in 39 cases; one patient (no. 19) showed a normocytic anemia, while in the remaining 11 cases the cell size was not specified. However, macrocytosis may be assumed in the latter since the blood in each instance was said to present the typical picture of pernicious anemia. That the macrocytosis was often pronounced is apparent from the figures for the mean diameter of the erythrocytes or the mean corpuscular volume which were included in certain of the case reports. In one case, a mean erythrocyte diameter of 9.1 microns is recorded, while in another, cells measuring up to 17 microns in diameter were noted. A mean corpuscular volume of over 120 cubic microns was not unusual.

Hyperchromia was present in 32 of the 42 cases in which figures are available. The color index varied from 0.90 to 2.08 with values above 1.30 in 18 of the cases.

As in true pernicious anemia leucopenia was an extremely common finding. In 30 of 36 cases in which the leucocyte count was recorded, values of 6,000 white blood cells per cubic millimeter or lower were reported, and in 23 of these cases the leucocyte count was 5,000 or below.

Gastric Analysis. The results of gastric analysis were given in 36 cases, of which 17 (47 per cent) showed free hydrochloric acid in the gastric juice. This percentage would probably be considerably higher had more of the patients who showed achlorhydria after a test meal received histamine. In Table III the presence or absence of free hydrochloric acid in the gastric juice is tabulated with respect to the type of specimen examined.

The presence of free hydrochloric acid in the gastric juice of such a large percentage of these cases sharply demarcates this form of macrocytic anemia from true pernicious anemia where complete achlorhydria, even after stimulation with histamine, is the rule. The results of the gastric analyses in this group of patients are comparable to those obtained in patients with sprue (Miller and Barker).

Direct tests for the presence of Castle's intrinsic factor in the gastric

juice were carried out in 2 cases of this series by means of gastric juice feeding experiments. In one (no. 40) conclusive proof of the presence of intrinsic factor was furnished, whereas in the other (no. 31) no intrinsic factor could be demonstrated. The excellent hematologic response of our first case (no. 49) and of case no. 51 to a diet rich in Castle's extrinsic factor was regarded as indirect evidence for the presence of intrinsic factor in the gastric juice of these patients.

Studies of Intestinal Absorption. It is unfortunate that intestinal absorption was studied in so few of these cases. The presence of fat in the stools was noted in 9 cases, whereas in 2 cases (nos. 5 and 51) the feces were said to contain no fat. In the authors' 2 cases, the absorption of fat from the intestine was studied by a more accurate

TABLE III

Gastric analysis in 36 cases

SPECIMEN OF GASTRIC JUICE	FREE HYDROCHLORIC ACID	
	Present	Absent
Fasting	3	
After test meal	6	12
After histamine	4	1
Vomitus	1	
Not specified	3	6
Totals	17	19

method described in detail elsewhere (Barker and Rhoads), i.e., the blood-lipid curve following the ingestion of a fat meal. Both patients gave essentially normal absorption curves which stand out in sharp contrast to the perfectly flat curves observed in patients with active sprue.

The absorption of glucose was studied by means of the oral glucose tolerance test in 4 cases (nos. 28, 33, 49 and 50). Although the first of these gave a flat blood-sugar curve comparable to that characteristic of sprue (Fairley; Hanes and McBride), the other 3 showed practically normal curves suggesting that glucose was readily absorbed in these cases.

Other observations upon the question of intestinal absorption have been included in the authors' two case reports. Suffice it to say

that the available data, scanty though they are, strongly suggest that defective intestinal absorption alone cannot explain the clinical picture presented by this group of patients.

PATHOLOGIC ANATOMY

Pathologic Diagnosis. Thirty-six of the 51 patients of this group died, and the diagnosis of intestinal stricture or anastomosis was established at autopsy in 31 of the 36; of the other 5 cases, the diagnosis

TABLE IV

Gastro-intestinal lesions

Strictures:		
Small intestine:		
Tuberculous	11	
Non-tuberculous	6	
Not specified	8	
Total		25
Large intestine:		
Tuberculous	1	
Non-tuberculous	2	
Carcinoma	1	
Post-operative	1	
Not specified	2	
Total		7
Anastomoses:		
Entero-enterostomy or entero-colostomy	13	
Gastro-jejuno-colic fistula	4	
Gastro-colic fistula	1	
Total		18
Diverticulosis		1
Total		51

was made at operation in 4, and by roentgen examination of the intestinal tract in one. Fifteen patients were alive at the time their cases were reported; in 13 of these the presence of a stricture or anastomosis was ascertained at operation; in the other 2 the diagnosis was made radiographically.

Lesions. The pathologic findings of principal interest were limited to the gastro-intestinal tract and the bone-marrow.

1. *Gastro-intestinal tract:* In Table IV the various types of gastro-intestinal lesions are summarized. Strictures of the intestine, either

single or multiple, were present in 32 cases, 25 in the small intestine and 7 in the colon. The majority of the strictures of the small intestine were located in the ileum; the jejunum was involved in a few instances. Of the strictures of the small intestines, 11 were definitely tuberculous in origin, 6 were said to be non-tuberculous, and in 8 the etiology was not specified. Certain of the non-tuberculous strictures were due to a non-specific terminal ileitis, as for example in 3 of the cases reported by Butt and Watkins. Incidently these authors described a macrocytic blood picture in several other cases of constrictive ileitis which are not included in the present review because the macrocytosis was not accompanied by definite anemia.

Anastomoses of one sort or another formed the basic abnormality in 18 cases. In 13 of these cases the anastomosis was either an entero-enterostomy or an entero-colostomy resulting from a surgical procedure which had been carried out for the relief of intestinal obstruction. Most of these operations had been performed to circumvent strictures or constricting adhesions which had developed subsequent to some previous operation, frequently appendectomy. In 2 of the 13 cases the anastomoses were complicated by fecal fistulas. 4 of the remaining 5 patients had gastro-jejuno-colic fistulas: in 3 of these the fistula developed after gastro-enterostomy for pyloric obstruction, whereas carcinoma of the stomach was responsible for the fistula in the fourth case. De Rivas' case (no. 27) was found at autopsy to have a gastro-colic fistula which had been created by error instead of the intended gastro-jejunostomy.

2. *Bone marrow:* Data on the appearance of the bone-marrow were furnished in 11 cases: 10 from post-mortem examination and one from sternal biopsy. Of the first 10, 9 showed a dark red hyperplastic marrow further described as "raspberry-liké" in one case and as "megaloblastic" in three cases; in one case (no. 39) the marrow was said to be fatty and aplastic. The authors' first case (no. 49) is the only one in which the marrow was studied by sternal biopsy before and after treatment with liver extract. The striking change from megaloblastic hyperplasia to an essentially normal marrow picture has already been described. There can be little doubt from the pathologic descriptions of these 11 cases that the bone-marrow picture in stricture

anemia is very similar to, if not identical with, that seen in true pernicious anemia and in the macrocytic anemia of sprue.

TREATMENT

The patients of this series have been divided into four groups according to the form of treatment they received: I, patients who received neither operative treatment nor liver therapy; II, patients treated by surgical means alone; III, patients treated with some form of liver therapy alone; IV, patients treated by both surgical means and liver therapy. Such a grouping serves to facilitate an evaluation of the results that have been obtained with different forms of therapy.

Group I. Patients who received neither operative treatment nor liver therapy: This group is made up of 23 patients who received neither liver therapy nor operative treatment as far as can be ascertained from the case reports. It is only fair to state that a number of the cases included in this group were reported very briefly and that therapy was not mentioned at all in several of these reports. Thus we cannot be certain that some specific form of therapy was not attempted in these cases. However, the majority of the cases comprising this group were observed before the advent of liver therapy.

Most of these patients simply received supportive treatment and succumbed to their illness or the complications thereof shortly after they first came under observation. Twenty-two of the twenty-three patients died and twenty-one were autopsied.

In view of the successful use of a milk diet in the treatment of certain cases of true pernicious anemia before the liver era (Barker and Sprunt), it is of interest that three patients of this group (Cases 4, 11 and 20) who were placed upon milk diets were distinctly benefited by such a dietary regime. All three showed remissions in the macrocytic anemia and, although two cases subsequently relapsed and died, the third patient (no. 20) was gaining weight and doing well at the time of the case report. In this case the blood picture had shown a complete change from the original macrocytosis and hyperchromia to a distinct microcytosis and hypochromia: before the milk diet, R. B. C. 1,750,000 with Hgb. 40%; after treatment, R. B. C. 4,620,000 with Hgb. 40%.

Two other cases were treated with colonic irrigations and arsenic;

one (no. 27) showed no improvement and died very shortly; the other (no. 6) experienced repeated remissions and relapses over a period of several years before suffering a fatal relapse.

Group II. Patients treated by surgical means alone (Table V): Of the nine patients who were subjected to some form of surgical pro-

TABLE V

Patients treated by surgical means alone

CASE NO.	LESION	OPERATION	RESULT
5	Stricture of jejunum	Entero-enterostomy	Died 2 days p-o
12	3 tuberculous strictures of small intestine	Resection of strictures	Died 12 hours p-o
15	Stricture of small intestine	Resection of stricture	Well 3 years p-o
23	3 strictures of lower ileum	Resection of 2 strictures	Died of complications, 5 weeks p-o; 3rd stricture found
28	Tbc. stricture of lower ileum	Ileo-colostomy	Marked blood rise, symptomatic improvement, and weight gain. Short follow-up
38	Post-operative strictures and operative anastomosis	Cecostomy	Died 3 weeks p-o
42	Operative jejuno-colostomy	Anastomosis taken down	Blood rose to normal; gain 45 lbs. in 3 months
46	Terminal ileitis with stricture	Ileo-colostomy	Anemia cleared up; no follow-up
48	Multiple fecal fistulas	Repair of fistulas; resection of sigmoid	Died p-o

cedure, five died so soon after operation that no conclusions can be drawn as to the effect of the operation on the blood picture. The four patients who survived showed striking symptomatic and hematologic improvement following operation. One patient (no. 15) was said

to have remained perfectly well for three years after the resection of a stricture of the small intestine, while another (no. 42) with a jejuno-colostomy showed a remarkable gain in weight and complete disappearance of the anemia within three months after the anastomosis had been closed.

In each of the other two cases (nos. 28 and 46) an ileo-colostomy was performed to circumvent strictures of the terminal ileum. The immediate results were excellent in both instances since the anemia cleared up completely. However, the shortness of the follow-up periods in these two cases gives little or no assurance that they did not later relapse in the manner so graphically illustrated by the authors' first case (no. 49—see under Group IV). When one is considering the advisability of an anastomotic operation in the treatment of intestinal stricture, it is well to recall that in 13 of the 51 cases of macrocytic anemia comprising the total series the anemia first developed *after* such operations had been performed to circumvent strictures.

Group III. Patients treated with liver alone (Table VI): This group consists of nine cases in which the anemia was treated without operation but with some form of liver therapy. It is to be noted that six patients in the group first developed macrocytic anemia after undergoing anastomotic operations which were designed originally to circumvent strictures.

Three of the patients in this group of nine died without evidence of improvement: case 26 died of carcinoma of the colon; case 39 of infection—the bone marrow was said to have been aplastic in this case; and case 32, a patient with a gastro-jejuno-colic fistula who was desperately ill, died the third day after the institution of liver therapy.

The remaining six patients showed striking improvement on liver therapy and maintained excellent health during the subsequent periods of observation. Three patients gave satisfactory responses to the oral administration of liver preparations; such responses may be accepted as evidence that there was no marked disturbance in intestinal absorption in these cases. It is of interest that one of these three patients (no. 31) had failed to improve on a preliminary course of 200 grams of raw beef a day, an excellent source of Castle's extrinsic factor. It was conclusively demonstrated that the gastric juice of this same patient contained no intrinsic factor. A fourth patient (no. 40) was first

TABLE VI

Patients treated with liver alone

CASE NO.	LESION	TREATMENT	RESULT
14	Post-operative strictures and anastomosis	(a) Arsenic, kefir milk, transfusions (b) Oral liver and L. E.	Remissions and exacerbations Well for one year; no further follow-up
26	Carcinoma with stricture of hepatic flexure	Oral liver and arsenic	Retic. rise but no blood rise; died 6 weeks later
31	Operative anastomoses and fecal fistulas	(a) 200 gm. raw beef q.d. (b) Oral L. E.	No improvement Prompt clinical improvement, retic. rise, and blood rise
32	Entero-enterostomy and ileo-colostomy	Whole liver and oral L. E.	Striking clinical improvement; blood returned to normal
35	Gastro-jejuno-colic fistula	Intramuscular L. E.	Died 3rd day
39	Post-operative adhesions constricting colon	Intramuscular L. E. and transfusions	Died of infection; aplastic bone marrow at autopsy
40	Operative anastomosis	(a) Intramuscular L. E. (b) Oral stomach preparation	Rapid rise in blood count Continued improvement; short follow-up
41	2 operative anastomoses	(a) Oral L. E. (b) Intramuscular L. E. 2 times a week	No response Complete remission; remained well during 3 year follow-up, on continued treatment
43	Operative ileo-colostomy	(a) Oral L. E., stomach yeast (b) Intensive intramuscular L. E. therapy	Little improvement Symptomatic and hematologic cure. Well during 1 year follow-up on continued treatment

treated parenterally with liver extract to which she responded well; her continued improvement after an oral preparation of desiccated

stomach had been substituted for the parenterally administered liver extract was regarded as evidence that she was capable of absorbing the anti-anemic principle from her intestinal tract. The last two patients (nos. 41 and 43) failed to improve on oral liver preparations, yet subsequently developed complete remissions on intensive parenteral liver extract therapy. Two possible explanations may be offered for such a course of events: 1) that the patients did not absorb the anti-anemic principle from the intestinal tract, or 2) that they required larger amounts of the principle than was supplied by oral dosage used.

Group IV. Patients treated by both surgical means and liver therapy (Table VII). Ten patients were treated with both operation and liver therapy at some time in the course of their illness. The failure of the patient to obtain relief from the first form of therapy that was instituted led to the adoption of further therapeutic measures in each of these cases.

In seven cases an attempt was first of all made to treat the condition by medical means such as a diet for sprue, the oral administration of yeast preparations, or some form of liver therapy. The blood picture showed considerable improvement in five of these cases (nos. 25, 33, 34, 45 and 47), but the persistence of gastro-intestinal symptoms in three cases made surgical intervention imperative. All three patients died shortly after operation: case no. 25 of diverticulitis, no. 34 of carcinoma of the stomach, and no. 47 after resection of the colon. One patient (no. 33) improved in every respect on a diet for sprue, supplemented with oral liver extract but relapsed when he stopped taking the liver extract. An operation was then performed, the gastro-jejuno-colic fistula was repaired, and he made a complete recovery without the aid of further liver therapy. In case no. 45 the macrocytic anemia improved under parenteral liver extract therapy, but considerable jaundice persisted. The patient was therefore operated upon and a long-loop intestinal anastomosis was taken down; following this procedure the jaundice cleared and the patient remained perfectly well with a normal blood picture during the two year follow-up period without further liver therapy.

The other two cases treated first by medical measures (nos. 44 and 50) showed no definite improvement in the blood picture under liver therapy. In case 44 the reticulocytes rose after the administration

TABLE VII

Patients treated by both surgical means and liver therapy

CASE NO.	LESION	TREATMENT	RESULT
24	2 operative anastomoses and fecal fistulas	(a) Operation: anastomoses taken down	Diarrhea ceased; anemia persisted
		(b) Oral L. E.	Anemia cured
		(c) Stopped L. E. and later resumed	Relapse and remission
		(d) Stopped L. E. for 2nd time	Developed combined system disease and died; autopsy showed obstruction from adhesions
25	Diverticulitis of intestine	(a) Oral L. E.	Blood remission; vomiting persisted
		(b) Operation: gastro-enterostomy and duodeno-enterostomy	Died 2 days after 2nd operation
33	Gastro-jejuno-colic fistula	(a) Milk diet	Temporary improvement
		(b) Sprue diet and oral L. E.	Marked symptomatic and hematologic improvement
		(c) Stopped L. E.	Relapse
		(d) Operation: gastro-jejuno-colic fistula repaired	Cure
34	Gastro-jejuno-colic fistula	(a) Sprue diet and oral L. E.	Blood improved; symptoms persisted
		(b) Operation: fistula repaired	Died with carcinoma of stomach
44	10 Tbc. strictures of lower jejunum	(a) Oral stomach and liver preparations; parenteral L. E.	Mild retic. response but no blood rise
		(b) Operation: anastomosis to circumvent strictures	Died soon afterwards with active tuberculosis
45	Operative anastomosis with long loop	(a) Oral L. E.	Temporary improvement; later relapse
		(b) Intramuscular L. E. 2 times a week	Blood rose to normal, jaundice persisted
		(c) Operation: anastomosis taken down	Complete cure without further liver—2 year follow-up

TABLE VII—*Continued*

CASE NO.	LESION	TREATMENT	RESULT
47	Ileo-colitis with strictures	(a) Parenteral L. E.	Blood responded, diarrhea persisted
		(b) Resection of colon	Died post-operative
49	Terminal ileitis with strictures	(a) Operation: ileo-colostomy to circumvent strictures	Temporary improvement in blood; later severe relapse
		(b) Sprue diet, oral and parenteral L. E.	Symptomatic and hematologic cure—2 year follow-up
50	Gastro-jejuno-colic fistula	(a) Sprue diet, Vegex, Ventriculin, oral and parenteral L. E.	Temporary weight gain; blood count variable; never entirely free of G-I symptoms
		(b) Operation: fistula repaired	Developed symptoms of pyloric obstruction
		(c) Operation: Polya gastro-enterostomy	Died 9 days later of complications
51	Post-operative adhesions constricting small intestine	(a) Operation: release of adhesions	Little change
		(b) Parenteral L. E.	Moderate blood rise
		(c) Vegex orally.	Marked improvement; gain of 40 lbs.; blood rose to normal; later relapse
		(d) Operation: resection of 60 cm. of strictured ileum	Blood rose to normal and remained so 8 months without liver or Vegex; then recurrence of G-I symptoms and anemia
		(e) Oral Vegex	Moderate improvement

of the anti-anemic principle but there was no rise in the blood count. An anastomosis was then performed to circumvent ten tuberculous strictures of the lower jejunum but the patient died with active tuberculosis shortly afterwards. Case 50, the second of our two cases, presented a difficult therapeutic problem as symptoms of peptic ulcer complicated the clinical picture. Under various forms of medical therapy the patient temporarily gained weight but his erythrocyte

count and hemoglobin level showed rather wide fluctuations and failed to return to normal. He was therefore subjected to operation, and the gastro-jejuno-colic fistula was taken down. Symptoms of pyloric obstruction and bleeding then developed, necessitating a second operation of the Polya type, and the patient died of complications nine days later.

In three cases (nos. 24, 49, and 51) the patients were first treated by surgical means. The failure of the operative treatment to relieve symptoms completely led to the subsequent institution of some form of liver therapy. The first of these patients (no. 24) underwent an extensive corrective operation for the repair of two intestinal anastomoses and several fecal fistulas. Diarrhea which had been troublesome before operation ceased, but the macrocytic anemia persisted until the patient had received liver extract by mouth. A blood remission then occurred and was maintained as long as the patient continued to take the liver extract. When he stopped taking liver extract the anemia recurred only to clear up again when liver therapy was resumed. The patient eventually stopped taking liver extract one more and developed a severe macrocytic anemia with combined degeneration of the spinal cord of which he died. This patient is of particular interest since the presence of free hydrochloric acid in his gastric juice would seem to rule out a coincidental "idiopathic" pernicious anemia.

The course of events in case 49, the first of our two cases, has been described in detail above. An anastomosis between the ileum and the transverse colon was first performed to circumvent the strictured terminal ileum. The mild macrocytic anemia present before operation temporarily disappeared after the anastomosis was performed, only to recur in a much more severe degree several months after operation. The relapse of the anemia was accompanied by diarrhea, flatulence, and glossitis. The anemia and gastro-intestinal symptoms cleared up entirely on a strict anti-sprue regime supplemented by parenteral liver extract and the patient has continued in excellent health for the past two years through strict adherence to the therapeutic program that was outlined for him.

Case 51, treated alternately with operations and medical therapy,

experienced repeated remissions and relapses as shown in the table. The development of fresh constricting adhesions was apparently responsible for the occurrence of the relapses.

From a study of this group of ten cases which were treated by both medical and surgical measures the complexity of the therapeutic problems which confront the physician becomes apparent at once. It is obvious that no single form of therapy will prove effective for all cases and that each patient presents an individual problem in therapy.

General Conclusions on Treatment: Certain conclusions may be drawn from this analysis of the results obtained with the various forms of therapy that have been employed in the treatment of "stricture anemia": 1) without either operation or liver therapy the prospect for improvement is very slight; 2) operations designed to correct the intestinal lesions are necessarily difficult procedures attended by a high operative mortality; 3) an operation successful in eliminating the mechanical abnormality may or may not be followed by complete cure; 4) the resection of a stricture or the restoration of the normal continuity of the bowel (in cases where an anastomosis is the offending lesion) is more likely to be attended by success than is an anastomotic operation designed to circumvent a stricture; 5) although liver therapy may bring about improvement in the blood picture, such therapy alone cannot be expected to relieve gastro-intestinal symptoms which are due to obstructive lesions in the intestinal tract; 6) surgical intervention is indicated in all cases with strictures and in young patients with anastomoses; preliminary liver therapy may serve to alleviate the anemia and thus reduce the operative risk in such cases; 7) liver therapy alone is indicated in older patients with well-functioning anastomoses where the operative risk is often extremely poor.

DISCUSSION

Two cases of macrocytic anemia in association with intestinal anastomoses have been reported in detail and 49 cases of a similar type of anemia occurring in patients with intestinal strictures or anastomoses have been collected from the literature. We have analyzed these cases from the standpoint of symptomatology, hematology, pathology, and treatment.

It is our impression that these cases do not represent a simple

coincidence of an intestinal lesion and "idiopathic" pernicious anemia in most (if in any) of the patients of this group. Three points may be offered in support of this impression: the gastric juice of a large number of the patients contained free hydrochloric acid; in one case the intrinsic factor of Castle was present in the gastric juice in normal amounts as shown by direct test, whereas in two other cases indirect evidence suggested that the gastric juice contained the intrinsic factor; and finally, most important of all, in six cases the surgical correction of the intestinal abnormality was followed by disappearance of the anemia without the aid of liver therapy.

If, then, coincidental "idiopathic" pernicious anemia (due to the absence of the intrinsic factor) can be dismissed as an explanation for the anemia in many if not all of these cases, other possible etiologic mechanisms for the production of macrocytic anemia must be considered. These include: 1) deficient absorption of the hematopoietic principle such as occurs in sprue; 2) diets deficient in the extrinsic factor; 3) disease of the liver; 4) failure of interaction between the intrinsic and extrinsic factors in the gastro-intestinal tract or destruction of the hematopoietic principle through abnormal bacterial activity in the intestine; and 5) the absorption of hemotoxic substances from the intestinal tract. It is extremely difficult to place a given case of macrocytic anemia in any one of the above categories since the situation is usually a complicated one and a combination of two or more factors undoubtedly plays a rôle in the majority of the cases. Nonetheless, it may prove of some interest to take up in order these five possibilities in an attempt to determine how much of a rôle each of these factors may have played in the etiology of the group of macrocytic anemias under consideration in this paper.

A rather strong case can be made out for the view that the patients of this group were suffering from a macrocytic anemia as the result of deficient absorption of the hematopoietic principle such as is thought to occur in sprue. It seems quite possible that the enteritis set up by the intestional stagnation that so often occurs above strictures or in short-circuited loops of bowel may interfere with the absorption of this substance. This explanation, favored by a number of authors, must be given serious consideration at least in certain of the cases where absorption of glucose, fat, and the active principle of liver was

shown to be impaired. Nevertheless, it could scarcely apply to all of the cases in this group, because in the majority of the cases in which intestinal absorption was studied, the results of the tests were surprisingly good.

As for the second possibility, unfortunately little was said in the case reports about the dietary of the patients of this group. In the two cases that we observed personally the anemia developed in spite of a normal intake of food and vitamins. It seems unlikely that deficiency of the extrinsic factor played more than a secondary etiologic rôle.

The occurrence of macrocytic anemia in association with disease of the liver is well established (Rosenberg, Wintrobe), but it is unusual to see a very marked degree of anemia under such circumstances. Although hepatic dysfunction undoubtedly was a factor in certain of the cases, there was little to suggest that this was of major importance. In our two cases conclusive evidence of liver damage was not found by any tests of liver function that were employed.

None of the etiologic mechanisms so far discussed furnishes a completely satisfactory explanation of the cases of macrocytic anemia under discussion. This leaves for consideration the last two possibilities: 4) failure of formation of the hematopoietic principle or destruction of the principle in the gastro-intestinal tract through abnormal bacterial activity, and 5) the absorption of toxic products of bacterial putrefaction in amounts too great to be neutralized by the normal detoxifying mechanisms of the body. These two possibilities will be discussed together because they rest upon a common basis, namely excessive bacterial activity in the intestinal tract.

Although the idea that the absorption of hemotoxic substances from the intestinal tract may be responsible for the development of "idiopathic" pernicious anemia is now an obsolescent theory, in the cases of macrocytic anemia associated with intestinal strictures and anastomoses such a theory must be given serious consideration. Hence it might be well to review briefly the evidence that has accumulated to support such a view.

When Faber in 1895 first called attention to the association of "pernicious anemia" with a stricture of the small intestine, he suggested that the anemia resulted from the absorption of a poison from the

stagnant bowel contents. Meulengracht (1921) found at autopsy in a case of severe "pernicious anemia" associated with a tuberculous stricture of the ileum that the entire small intestine was heavily infected with bacteria. Comparing his case with five similar cases from the literature, he drew the following conclusions: 1) pernicious anemia may develop on the basis of benign intestinal strictures; 2) the anemia is probably due to the absorption of hemotoxic substances from the dilated and infected portion of the bowel above the stricture; 3) such cases support the theory of the intestinal origin of cryptogenetic pernicious anemia.

In 1927 Seyderhelm, Lehmann, and Wichels succeeded in simulating the clinical picture of stricture anemia in four of ten dogs in which they had produced intestinal strictures at operation. The anemia proved fatal in two of these dogs and post-mortem examination revealed marked stagnation and putrefaction of the bowel contents above the stricture with a luxuriant growth of bacteria throughout the small intestine. In the case of the dogs which failed to develop anemia the small intestine above the stricture remained practically sterile. The authors concluded that the absorption of toxic end-products of bacterial putrefaction was responsible for the development of the anemia. More recently Horster has added further experimental evidence along the same lines. He observed that dogs in which he had produced intestinal strictures or blind pouches developed an abundant flora of gram-negative bacilli in the upper intestinal tract and even in the stomach. Such dogs showed marked indicanuria, severe anemia with hemosiderin deposits in the liver and spleen, and evidence of liver damage. These changes could be prevented by feeding trichlorcresol to check the bacterial growth; furthermore the symptoms cleared up after resection of the blind pouch or stricture.

"Idiopathic" pernicious anemia was treated by means of ileostomy and colonic irrigations by Seyderhelm (1922) with interesting results. Complete blood remissions of five and seven months respectively occurred in two of three patients so treated, but relapse followed closure of the ileostomy. After ileostomy the drainage from the ileum became practically sterile in these two cases, whereas in the third case (a patient who derived no benefit from ileostomy) the drainage remained foul and grossly infected and at autopsy a heavy bacterial

growth was noted throughout the small intestine. It was scarcely unreasonable for Seyderhelm to suppose that the improvement in the first two cases had resulted from the eradication of intestinal putrefaction.

Seyderhelm's observations were confirmed in 1925 by Dixon, Burns and Giffin in their report of six cases of pernicious anemia treated by ileostomy. Four of the six cases showed at least temporary blood remissions while symptomatic improvement was striking in several. These authors suggested that ileostomy, besides excluding the colon, presumably establishes more complete drainage of the ileum. Completely in accord with these observations are the bacteriologic studies of Otto and others who have described a luxuriant pathologic flora of colon bacilli throughout the entire gastro-intestinal tract of patients suffering from pernicious anemia. The above work represents only a small portion of the clinical and experimental data that has accumulated to make out a very strong case for the enterotoxic theory of pernicious anemia.

With the classic discovery of liver therapy for pernicious anemia by Minot and Murphy in 1926, soon to be followed by Castle's (1929) fundamental observations on the relation of the intrinsic (gastric) and extrinsic (food) factors to the hematopoietic principle of liver, the toxic theory gave way to the overwhelming evidence that pernicious anemia was a deficiency disease, or at least a "conditioned deficiency state." However, the mechanism of action of the liver principle is still far from clear. It has been postulated that liver supplies a substance necessary for the proper maturation of the erythrocytes. Such a substance must possess the additional properties of preventing or curing the other changes that occur in pernicious anemia such as the atrophy of the mucosa of the tongue and stomach and the degenerative lesions in the spinal cord. Furthermore, if we accept the view that pernicious anemia is a hemolytic anemia, a hypothesis which is strongly supported by the hyperbilirubinemia and the increased excretion of urobilin that occur regularly during the relapse phase of the disease, we must attribute still another property to the liver principle,—that of inhibiting hemolysis. It would then appear that this principle must exert its effect at several different sites in the body, yet it has already been demonstrated (Dakin and West) that a very small

amount of the material is necessary to bring about improvement in all of the various manifestations of pernicious anemia. It is certainly tempting at least to assume that the liver principle might exert its effect at a single point: for example, in the liver itself or in the intestinal wall.

If the site of action were the liver, it seems possible that the antianemic principle may promote the detoxification of some injurious substance or substances absorbed from the intestinal tract. Detoxification of certain products of intestinal putrefaction such as indol and skatol has long been recognized as one of the important functions of the liver. The work of Rhoads and his co-workers indicates that a severe hemolytic anemia without reticulocytosis may be produced in dogs fed a deficient diet by the oral administration of indol and that this anemia may be prevented or cured by the oral administration of liver extract. Furthermore, Horster has shown that the various manifestations of intestinal intoxication (including anemia, liver damage, and hemosiderosis) which developed in his dogs with intestinal strictures or blind pouches could be inhibited or alleviated by injections of liver extract. Clinically macrocytic anemia commonly occurs in association with extensive disease of the liver. The usual explanation given for macrocytic anemia of this type is the failure of the damaged liver to store adequate amounts of the hematopoietic principle. However, it has been a common experience to find that in certain cases the macrocytic anemia of liver disease fails to respond well to therapy with liver extract. This observation suggests that the liver itself must be functioning well if the active principle of the injected extract is to work effectively. It does not require a wide departure from the established facts to look upon the manifestations of pernicious anemia as resulting from the penetration of some toxin beyond the normal liver barrier whence it might exert its effects at widely scattered points in the body.

On the other hand there is certain evidence that the liver principle may act directly in the intestinal wall. Various workers (Fairley; Hanes and McBride; Barker and Rhoads) have shown that the absorption of glucose and fat in cases of sprue is far better after treatment with liver extract than before such treatment. If, as it appears, the liver principle can increase the permeability of the intestinal wall for

certain necessary food substances, it is quite conceivable that it may decrease the permeability of the wall to other substances, as for example toxic materials, or promote the detoxification of such materials in the intestinal wall.

The above discussion has been presented in the hope of reviving interest in the possibility that intestinal intoxication may be an important factor in the pathogenesis of pernicious anemia and related macrocytic anemias. We do not wish to create the impression that we are disputing the current view that a deficiency state is of primary importance in pernicious anemia. It must be pointed out, however, that the mode of action of the hematopoietic principle has not been explained. We are merely suggesting an explanation of the mechanism of action of liver therapy which is totally different from the generally accepted one. In other words, instead of regarding the active principle of liver as supplying a building-stone for the proper maturation of the red blood corpuscles, we feel that there is abundant evidence to support the contention that the liver principle may be necessary to promote the proper detoxification of some chemical compound or compounds, which if unneutralized might give rise to a variety of harmful changes throughout the body. This hypothesis is not an entirely novel one, for in addition to a number of European workers, Dock in this country has recently expressed himself as favoring such a stand. On the basis of such an hypothesis, the macrocytic anemias associated with intestinal strictures or anastomoses might be regarded as resulting from a state of abnormal intestinal toxemia which could be overcome either by removing the cause for the stagnation and putrefaction of the intestinal contents or by supplying excessive amounts of the liver principle to detoxify the excess of toxins absorbed. The development of true "idiopathic" pernicious anemia, on the other hand, would depend upon the failure of the body to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substances normally absorbed from an intestinal tract where stagnation is not necessarily a factor.

SUMMARY AND CONCLUSIONS

Two cases of macrocytic anemia in association with intestinal anastomoses have been reported in detail and 49 cases of a similar type of

anemia occurring in patients with intestinal strictures or anastomoses have been reviewed from the literature.

From an analysis of these cases the conclusion seems justified that we are dealing with a distinct disease entity and not with a simple coincidence of "idiopathic" pernicious anemia and an intestinal lesion.

The pathogenesis of this form of macrocytic anemia appears to be intimately bound up with stagnation and putrefaction of the intestinal contents, resulting perhaps in the absorption of toxic substances. Consequently, successful treatment of the anemia usually depends upon the surgical removal of the cause for the intestinal stagnation, although intensive therapy with liver extract may bring about clinical and hematologic improvement in certain cases.

The relationship of macrocytic anemias of this type to "idiopathic" pernicious anemia has been discussed. It is suggested that the hematopoietic principle of liver may exert its effect, not by supplying a building-stone for the proper maturation of erythrocytes, but by promoting the detoxification of injurious substances absorbed from the intestinal tract.

We wish to express our appreciation to Dr. F. H. Bethell, Dr. W. B. Castle, Dr. G. R. Minot, Dr. C. H. Watkins, and Dr. L. G. Zerfas for furnishing us with additional data on certain of the cases included in the review.

BIBLIOGRAPHY

BARKER, A. E., AND HUNTER, W.: A case of pernicious anemia following on traumatic stricture of the small intestine. *Lancet* **2**: 164–167, (July 21) 1900.

BARKER, L. F., AND SPRUNT, T. P.: The treatment of some cases of so-called "pernicious anemia". A regimen that has been found helpful. *J. A. M. A.* **69**: 1919–1925, (Dec. 8) 1917.

BARKER, W. H., AND RHOADS, C. P.: The effect of liver extract on the absorption of fat in sprue. *Am. J. M. Sc.* **194**: 804–810, (Dec.) 1937.

BECKER, G.: Liver treatment in diseases with a blood picture of pernicious anemia. *Acta Med. Scandinav.* supp. **34**: 70–74, 1930.

BETHELL, F. H.: Unpublished data.

BORCHEGREVINK, O.: Multiple tuberkulose tyntarmstrikturer. *Norsk. Magaz. f. Laegevidensk.* **59**: 57–68, 1898.

BREMER, F. W.: Über die Pathogenese der perniziösen Anämie. *Klin. Wchnschr.* **11**: 1657–1661 (Oct. 1) 1932.

BRETSCHNEIDER, A.: Latente Tuberkulose des Darms und der mesenterialen Lymphdrüsen als Ursache eigenartiger hämatologischer Syndrome. *Berlin. klin. Wchnschr.* **48:** 2249–2251, 1911.

BUTT, H. R., AND WATKINS, C. H.: Occurrence of macrocytic anemia in association with lesions of the bowel. *Ann. Int. Med.* **10:** 222–232, (Aug.) 1936.

CASTLE, W. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. *Am. J. M. Sc.* **178:** 748–764, (Dec.) 1929.

Idem: Personal communication to the authors, 1937.

CASTLE, W. B., HEATH, C. W., AND STRAUSS, M. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. IV. *Am. J. M. Sc.* **182:** 741–764, (Dec.) 1931.

CHRISTOPHER, F.: Vicious jejuno-colostomy with chronic ileac obstruction. *Am. J. Surg.* **29:** 124–127, (July) 1935.

DAKIN, H. D., AND WEST, R.: Observations on the chemical nature of the hematopoietic substance occurring in liver. *J. Biol. Chem.* **109:** 489–522, (May) 1935.

DERIVAS, D.: Discussion on sprue. *J. A. M. A.* **95:** 1964, (Dec. 27) 1930.

DEUTSCH, M.: Ein Fall hyperchromer Anämie infolge einer Dünndarmstriktur bei einem Kind. *Med. Klin.* **22:** 1145–1146, (July 23) 1926.

DIXON, C. F., BURNS, J. G., AND GIFFIN, H. Z.: Pernicious anemia following ileostomy. *J. A. M. A.* **85:** 17–20, (July 4) 1925.

DOCK, W.: The importance of hemolysis in the pathogenesis of macrocytic anemia. *Medical Papers dedicated to Dr. Henry A. Christian*, Baltimore, Waverly Press, Inc. 1936, pp. 545–558.

ÉMILE-WEIL, P., STIEFFEL, AND BOUSSER: Un cas d'anémie grave aplastique au cours de sténoses intestinales. *Sang.* **7:** 540–545, 1933.

FABER, K.: Perniciöse Anämie bei Dünndarmstrikturen. *Berlin. klin. Wchnschr.* **34:** 643–646, 1897. (Case previously published in Danish literature, 1895).

FAIRLEY, N. H.: Tropical sprue with special reference to intestinal absorption. *Tr. Roy. Soc. Trop. Med. & Hyg.* **30:** 9–32, (June) 1936.

FAIRLEY, N. H., AND KILNER, T. P.: Gastro-jejuno-colic fistula, with megalocytic anemia simulating sprue. *Lancet* **2:** 1335–1341 (Dec. 19) 1931.

GLUZINSKI, A.: Die schweren Formen der Anämie im Zusammenhange mit der Tuberkulose samt einigen Bemerkungen über die Tuberkulose tierischen Ursprungs (Typus bovinus) bei den Menschen. *Beitr. z. Klin. d. Tuberkulose.* **21:** 331–357, 1911.

HANES, F. M., AND MCBRIDE, A.: Identity of sprue, non-tropical sprue, and celiac disease. *Arch. Int. Med.* **58:** 1–16, (July) 1936.

HARTMANN, E.: Hyperchrome Anämie bei Stagnation des Darminhaltes in einer Seitentasche des Dünndarms. *Klin. Wchnschr.* **8:** 1359–1360, (July 16) 1929.

HAWKSLEY, J. C., AND MEULENGRACHT, E.: Intestinal stricture and its association with pernicious anemia. *Lancet*, **2:** 124–125, (July 18) 1936.

HEATH, C. W., AND FULLERTON, H. W.: The rate of absorption of iodide and glycine from the gastro-intestinal tract in normal persons and in disease conditions. *J. Clin. Invest.* **14:** 475–481, (July) 1935.

HOLST, P. F. 1896. (Cited by Meulengracht, 1921).

HORSTER, H.: Experimentelle Therapie bei intestinaler Autointoxication. *Ztschr. f. d. ges. Exp. Med.* **95:** 514–518, 1935.

HURST, A. F.: A case of Addison's anemia with subacute combined degeneration of the spinal cord and normal gastric secretion following chronic obstruction of the ileum. *Guy's Hosp. Rep.* **83:** 47–52, 1933.

KRETZ, J.: Ein Fall von Zökumstenose und hyperchromer Anämie. *Med. Klin.* **21:** 886–888, (June 12) 1925.

LITTLE, W. D., ZERFAS, L. G., AND TRUSLER, H. M.: Chronic obstruction of the small bowel; result of 2 entero-enterostomies and apparently the cause of pernicious anemia. *J. A. M. A.* **93:** 1290–1291, (Oct. 26) 1929.

MEULENGRACHT, E.: Darmstriktur und perniziöse Anämie. *Arch. f. Verdauungskr.* **28:** 216–225, 1921.

Idem: Darmstrikturen und perniziöse Anämie. Darmresektion. *Acta med. Scandinav.* **56:** 432–442, 1922.

Idem: Pernicious anemia in intestinal stricture. *Acta med. Scandinav.* **72:** 231–240, 1929.

Idem: Behandlung von Hämatemesis und Meläna mit uneingeschränkter Kost. *Wien. klin. Wchnschr.* **49:** 1481–1485, (Dec. 4) 1936.

MILLER, D. K., AND BARKER, W. H.: The clinical course and treatment of sprue. *Arch. Int. Med.* **60:** 385–414, (Sept.) 1937.

MINOT, G. R.: Anemia and the gastro-intestinal tract; synopsis. *Am. J. Digest. Dis. & Nut.* **3:** 643–646, (Nov.) 1936.

MINOT, G. R., AND MURPHY, W. P.: Treatment of pernicious anemia by a special diet. *J. A. M. A.* **87:** 470–476 (Aug. 14) 1926.

NARBESHUBER, K.: Strikturanämie und Leberdiät. *Med. Klin.* **27:** 389–391, (Mar. 13) 1931.

OTTO, H.: Die Gastroduodenalflora bei Anaemia Gravis. *Ztschr. f. klin. Med.* **126:** 265–291, 1933.

QUICK, A. J.: The synthesis of hippuric acid: a new test of liver function. *Am. J. M. Sc.* **185:** 630–635, (May) 1933.

RHOADS, C. P., AND MILLER, D. K.: Induced susceptibility of the blood to indol. *J. Exp. Med.* **67:** 273–297, (Feb.) 1938.

RHOADS, C. P., BARKER, W. H., AND MILLER, D. K.: The increased susceptibility to hemolysis by indol in dogs fed deficient diets. *J. Exp. Med.* **67:** 299–308, (Feb.) 1938.

RICHARDSON, W.: Pernicious anemia due to enteroenterostomy. Report of a case cured by reoperation. *N. Eng. J. Med.* **218:** 374–376, (Mar. 3) 1938.

ROSENBERG, D. H.: Macrocytic anemia in liver disease, particularly cirrhosis; observations on incidence, course, and reticulocytes, with a correlated study of gastric acidity. *Am. J. M. Sc.* **192:** 86–97, (July) 1936.

SCHERER, E.: Hyperchrome Anämie und Dünndarmstriktur. *Klin. Wchnschr.* **9:** 790–791, (April 26) 1930.

SCHLESINGER, A.: Nachweis des Antiperniciosa—Prinzips in Magensaft einer Patientin mit perniziös-anämischem Blutbild bei Dünndarmstenose. *Klin. Wchnschr.* **12:** 298–300, (Feb. 25) 1933.

SCHMIDT, A.: Severe anemia connected with gastro-intestinal diseases. *Am. J. M. Sc.* **148:** 313–323, (Sept.) 1914.

SCHMIDT, W.: Dysfunktion des Intestinaltraktus und perniziöse Anämie. *Ztschr. f. klin. Med.* **106:** 337–353, 1927.

SEYDERHELM, R.: Die Pathogenese der perniziösen Anämie. *Ergeb. d. inn. Med. u. Kinderk.* **21:** 361–419, 1922.

SEYDERHELM, R., LEHMANN, W., AND WICHELS, P.: Intestinale perniziöse Anämie beim Hund durch experimentelle Dünndarmstriktur. *Krankheitsforschung* **4:** 263–279, 1927.

STRANDELL, B.: Pernicious anemia; study of 117 cases. *Acta med. Scandinav.* supp. **40:** 1–124, 1931–32.

STRAUSS, M. B.: The rôle of the gastro-intestinal tract in conditioning deficiency disease. *J. A. M. A.* **103:** 1–4, (July 7) 1934.

STURGIS, C. C.: Present status of pernicious anemia; experience with 600 cases over 8 years. *Ann. Int. Med.* **10:** 283–289, (Sept.) 1936.

SZCZEPANSKI, Z.: Schwere perniziöse Anäemie und Tuberkulose. *Folia. Haemat. Zentralorgan* **21:** 366, 1923.

TAYLOR, G. W.: Intestinal diverticulosis, pernicious anemia, bilateral suprarenal apoplexy; report of a case. *N. Eng. J. Med.* **202:** 269–271, (Feb. 6) 1930.

WALLIS, C., AND WARFVINGE. 1893 (cited by Meulengracht, 1921).

WIECHMANN, E., AND ZINSSER, F.: Darmstriktur und perniziöse Anämie. *München. med. Wchnschr.* **73:** 372–373, (Feb. 26) 1926.

WINTROBE, M. M.: Relation of disease of the liver to anemia. *Arch. Int. Med.* **57:** 289–306, (Feb.) 1936.

ZADEK, I.: Darmulcera und Strikturen bei perniziöser Anämie. *München. med. Wchnschr.* **73:** 2165–2166, (Dec. 17) 1926.

FIG. 3. *Case no. 49. Photomicrographs of the sternal bone marrow.* Mallory's eosin and methylene blue. (A) Before treatment. The marrow is hyperplastic with defective maturation of both erythroid and myeloid cells. × 250. (B) After treatment with diet for sprue and liver extract. Note the decrease in cellularity and the increase in fat. Maturation has returned to normal with normoblasts and polymorphonuclear leucotyes predominating. × 250.

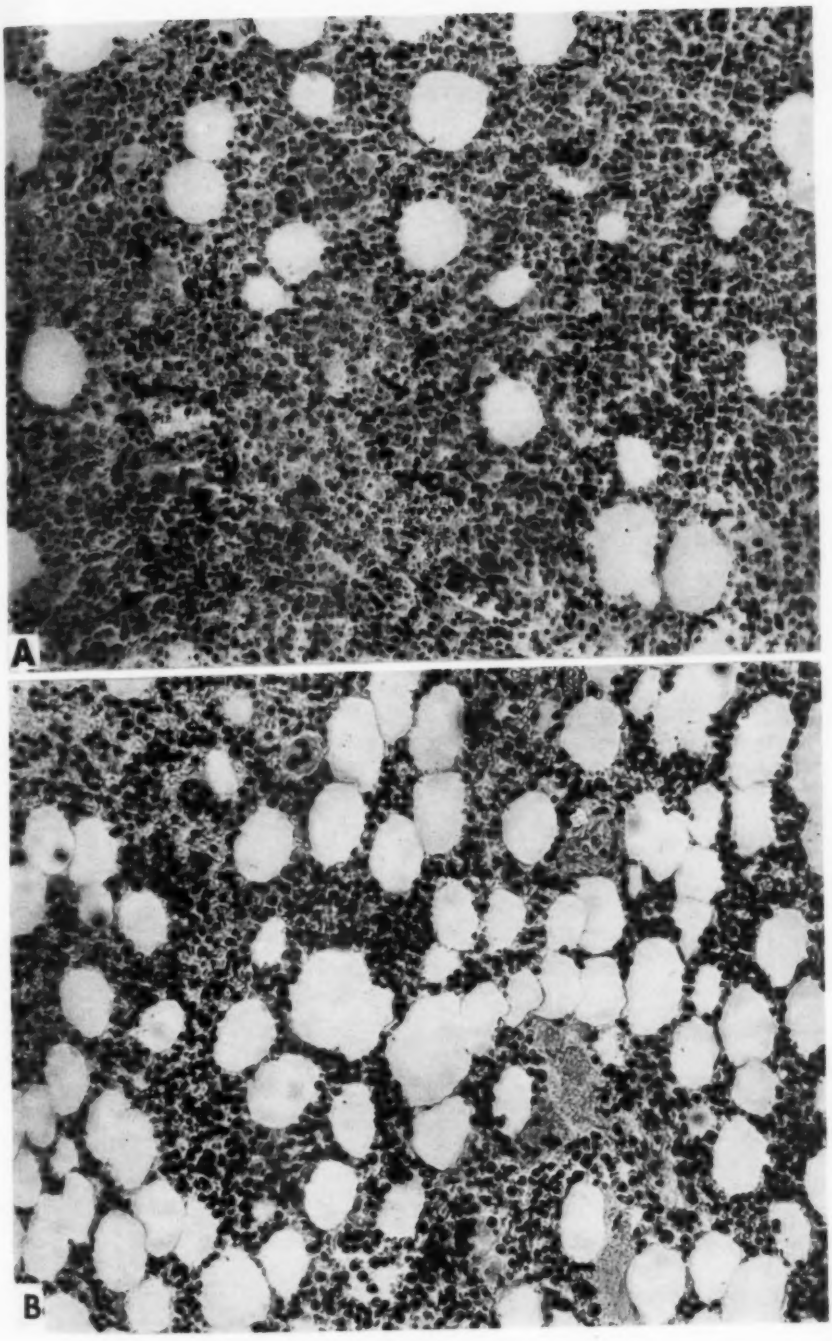

FIG. 3

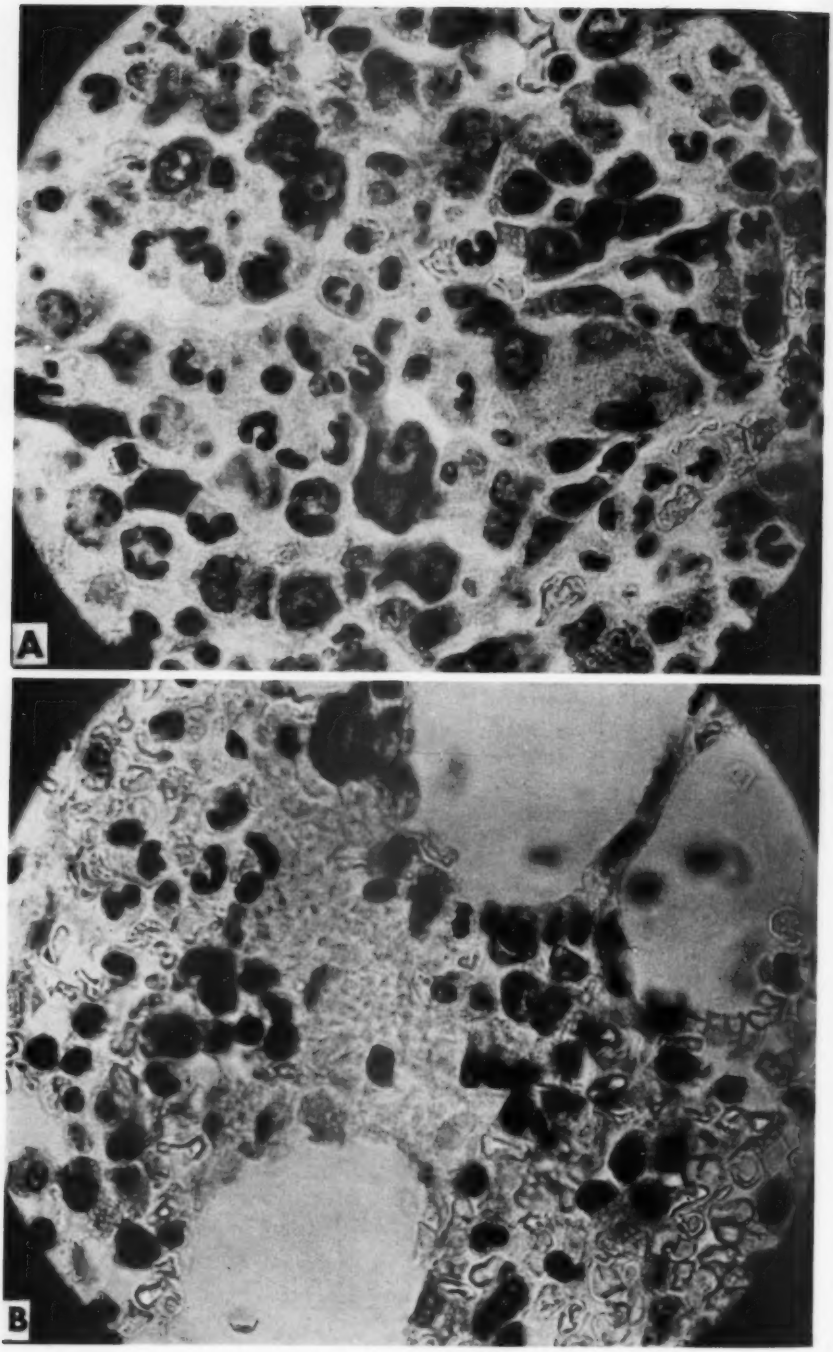

FIG. 4. (A) The same as Fig. 3 A. × 1000
(B) The same as Fig. 3 B. × 1000

DIABETES, INSULIN ACTION, AND THE RESPIRATORY QUOTIENT[1]

EDWARD M. BRIDGE AND ELEANOR A. WINTER

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital

Submitted for publication January 4, 1939

Although the effectiveness of insulin in ameliorating the symptoms of diabetes is one of the most striking phenomena in the field of medicine, few undisputed facts are known concerning the nature of the underlying disturbance, or the mechanism through which insulin produces its effect. The view is commonly held among clinicians that the fundamental defect in diabetes is an inability to utilize carbohydrate materials, and that the level of the blood sugar serves as a satisfactory guide to the intensity of this disturbance. Insulin, because of its strikingly beneficial effects, is assumed to be a specific agent which makes possible satisfactory carbohydrate utilization.

That so simple an explanation of diabetes and insulin action is inadequate is evident from several well established facts. In the first place, carbohydrate is being utilized even in the complete absence of the pancreas. This fact was demonstrated by Mann and Magath (1) in the rapid fall of the blood sugar to hypoglycemic levels in completely diabetic dogs following removal of the liver. In the second place, in diabetes there is more than a mere inability to utilize ingested carbohydrate, for in its severe forms, more carbohydrate is excreted in the urine than is ingested; an actual overproduction of glucose is occurring. And finally, as will be pointed out below, no relationship is demonstrable between the quantity of insulin present in the body and the level of carbohydrate combustion as measured

[1] The study was made possible by a grant from Mead Johnson and Company, Evansville, Indiana.

The writers are indebted to Dr. Harriet Guild for permission to conduct the study on patients of her diabetic clinic at the Harriet Lane Home, and for her assistance in carrying out the program.

TABLE I

The blood sugar and respiratory quotient data obtained on diabetic patients during general regulatory treatment in a hospital

PATIENT	AGE	DATE	FASTING		MID A.M.		BEFORE LUNCH		MID P.M.		BEFORE SUPPER		LATE EVENING		INSULIN		REMARKS
			B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	Type*	Insulin Units†	
A. E.	13	12/ 3/37	147	.80	217	.84	153	.85	224	.80	142	.81	187	.81	Reg.	7–0–3	
A. E.	13	12/20/37	189	.88	246	.93	221	.91	240	.91	164	.90	144	.88	Prot.	6–0–0	Improved
D. L.	8	3/18/38	92	.76	319	.77	115	.87	92	.88	56	.94	134	.86	Reg.	18–8–6	No ketosis No reaction
D. L.	8	3/21/38	92	.83	407	.83	345	.81	369	.80	302	.83	313	.78	No insulin		Slight ketosis from 11:30 a.m. on; increasing to 2+
D. L.	8	3/22/38	111	.82	290	.83	114	.86	160	.81	160	.87	198	.87	Reg.	18–8–6	Decreasing ketosis; none after 12 noon
D. L.	8	4/ 5/38	71	.82	189	.86	49	.81	147	.81	62	.85	162	.86	Reg. Prot.	14 9 } 0–0	No ketosis No reaction
D. L.	8	4/ 7/38	98	.82	351	.81	306	.84	338	.80	321	.84	429	.84	No insulin		No ketosis
D. L.	8	4/ 8/38	224	.82	404	.80	189	.80	218	.79	128	.85	245	—	Reg. Prot.	14 9 } 0–0	No ketosis
M. H.	11	11/30/37	64	.83	69	.84	66	.83	126	.83	199	.80	252	.86	Reg. Prot.	18 20 } 0–0	Mild reaction at 12:30 p.m.
M. H.	11	12/ 9/37	57	.81	71	.86	64	.83	214	.82	284	.84	317	.84	Reg. Prot.	20 14 } 0–0	No ketosis No reaction
M. H.	11	3/ 8/38	199	.84	252	.85	110	.82	260	.81	258	.81	402	.80	Reg. Prot.	12 24 } 0–0	No ketosis
M. H.	11	3/10/38	71	.90	399	.79	423	.80	420	.81	375	.83	450	.75	No insulin		Ketosis from 2:30 p.m. increasing to 2+ by 7:30 p.m.

M. H.	11	3/11/38	273	.80	354	.81	208	.84	238	.80	267	.83	410	.71	Reg. Prot.	12 24 } 0-0	Height of ketosis at 10 a.m.; 3+ and 3+; disappeared by 8 p.m.
J. W.	12	2/ 2/38	411	.78	557	.76	493	.74	289	.78	199	.78	316	.74	Reg.	40-12-14	Ketosis from 8 a.m. on—varies from 4+ to 2+—highest after meals
J. W.	12	2/11/38	68	.86	101	.88	64	.83	76	.81	83	.82	190	.85	Reg. Prot.	35 30 } 0-0	Slight reaction a.c. (lunch)
J. W.	12	2/21/38	241	.77	306	.83	114	.80	220	.84	235	.82	321	.83	Reg. Prot.	30 30 } 0-0	Trace of acetone in mid afternoon—none in evening
J. M.	7	12/ 1/37	123	.77	66	.82	77	.79	111	.82	174	.88	163	.92	Reg. Prot.	13 15 } 0-0	No ketosis No reaction
J. M.	7	12/ 7/37	112	.83	167	.81	84	.82	202	.84	381	.83	411	.85	Reg. Prot.	13 17 } 0-0	Trace of ketosis between 5:30-8 p.m.
R. Z.	15	1/31/38	395	.78	319	.81	158	.80	216	.76	110	.80	174	.85	Reg.	56-5-15	Ketosis: 3+ early morning; 4+ at 10 a.m.—traces after other 2 meals
R. Z.	15	2/ 8/38	286	.79	276	.83	99	.79	136	.78	124	.81	239	.81	Reg. Prot.	45 32 } 0-0	Ketosis: 3+ midmorning; none after noon
R. Z.	15	2/11/38	287	.78	287	.81	140	.76	143	.82	113	.78	281	.79	Reg. Prot.	43 32 } 0-0	Trace ketosis midmorning; none after noon; trace in night specimen
I. K.	27	1/18/38	173	.79	195	.87	175	.91	139	.82	150	.78	240	.79	Reg. Prot.	5 25 } 0-0	No ketosis
I. K.	27	1/27/38	203	.84	243	.88	82	.83	224	.80	233	.80	258	.82	Prot.	25-0-0	No ketosis; no reaction

* *Reg.:* regular insulin. *Prot.:* protamine insulin.
† Insulin units recorded 0-0-0 to indicate morning, noon, and evening doses.

TABLE 1—*Concluded*

PATIENT	AGE	DATE	FASTING		MID A.M.		BEFORE LUNCH		MID P.M.		BEFORE SUPPER		LATE EVENING		INSULIN		REMARKS
			B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	B.S.	R.Q.	Type*	Insulin Units†	
C. C.	16	2/23/38	129	.87	120	.89	58	.93	156	.95	99	.92	212	—	Prot.	50–0–0	No ketosis; no reaction
C. C.	16	2/28/38	96	.91	211	.94	60	.91	121	.86	109	.88	222	.77	Prot.	50–0–0	No ketosis; no reaction
C. D.	10	12/15/37	78	.80	187	.88	60	.79	182	.83	238	.87	469	.87	Reg. Prot.	15 22 }0–0	No ketosis No reaction
C. I.	18	2/24/38	254	.79	241	.83	207	.86	125	.80	78	.79	110	.80	Reg.	48–24–30	No ketosis No reaction
M. C.	21	3/ 2/38	59	.87	229	.80	136	.82	143	.80	61	.80	134	.83	Prot.	30–0–0	No ketosis No reaction
W. M.	10	12/17/37	69	.85	260	.87	208	.92	328	.88	395	.90	433	.78	Reg. Prot.	10 27 }0–0	No ketosis
M. B.	57	11/29/37	114	.69	193	.76	132	.76	173	.77	131	.76	174	.77	Prot.	0–15–0	No ketosis

by the respiratory quotient. Obviously the fundamental defect of diabetes is more than the lack of a hormone which acts directly on carbohydrate causing its combustion.

PROCEDURES

The observations which comprise the present study were made on diabetic children and adults. None was in a state of acidosis or coma; all were being regulated in the usual manner by diet and insulin dosage while on the hospital wards. At the time of the study, in some, the diabetes was poorly controlled; in others it was regulated and the patients were ready for discharge. Some were receiving too much insulin and had occasional reactions; others were getting too little insulin and showed mild degrees of transitory ketosis. On three occasions insulin was omitted altogether for a 24-hour period. Such wide variations in the state of the disease and in the range of insulin dosage offered excellent opportunities for studying the influence of insulin on carbohydrate combustion.

The technical details were simple. By repeated tests all patients were thoroughly accustomed to the procedures and coöperated well. Following a period of rest in bed, expired air of ten-minute periods was collected in a Douglas bag and samples were taken for respiratory quotient determinations using the customary Haldane technique. Corrections were not made for protein metabolism, but each patient received a constant daily intake of protein which was divided approximately equally between the three meals. Capillary blood for sugar estimation was obtained after each respiration period and was analyzed by the Hagedorn-Jensen method (2). Usually six determinations of both blood sugar and respiratory quotient were made during a day, before meals, halfway between meals, and before going to sleep at night. The urine was examined frequently for sugar and ketones. In all 13 patients have been observed throughout a total of 30 days.

RESULTS

The results of the study appear in Table I. For the purpose of analysis and discussion the findings have been divided into several groups representing the relationship of the respiratory quotient (1) to general improvement of the diabetes, (2) to blood sugar variations,

(3) to hypoglycemia, and (4) to hyperglycemia. Since space does not permit all the data to be presented graphically, only examples from each group appear in the charts.

A single opportunity presented itself for observing the effects of *improvement* of the diabetes on the respiratory quotient. Patient I, A. E., a boy of 13, entered the hospital shortly after his disease had been discovered. During the period between the two sets of observations, his general well-being improved, he gained 1.6 kilos in weight, and it became possible to reduce the total insulin from ten to six

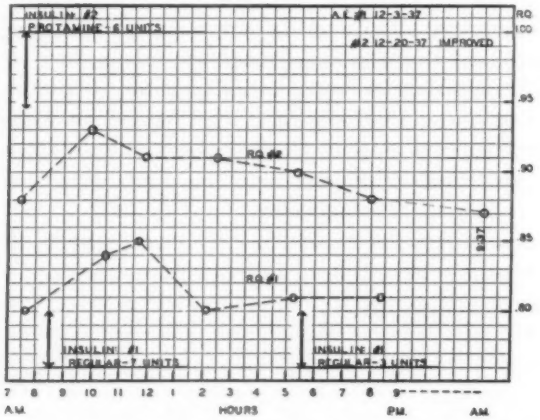

CHART 1. Data obtained in the study of a diabetic boy showing an increase in the general level of the respiratory quotient throughout the day following two weeks of hospital treatment. A corresponding lowering of the blood sugar level did not occur.

units a day. The dietary carbohydrate was increased from 175 to 185 grams a day in the interval between the two tests. As will be seen from Chart 1, (A. E. 12–3–37 and 12–20–37) this improvement was accompanied by a rise in the general level of the respiratory quotient throughout the day. The data in Table I, however, show this to have occurred without a significant reduction in the blood sugar level. Such a rise in the R.Q. is to be expected since diabetics have frequently been observed to improve in their ability to utilize carbohydrate when treated with insulin over long periods of time.

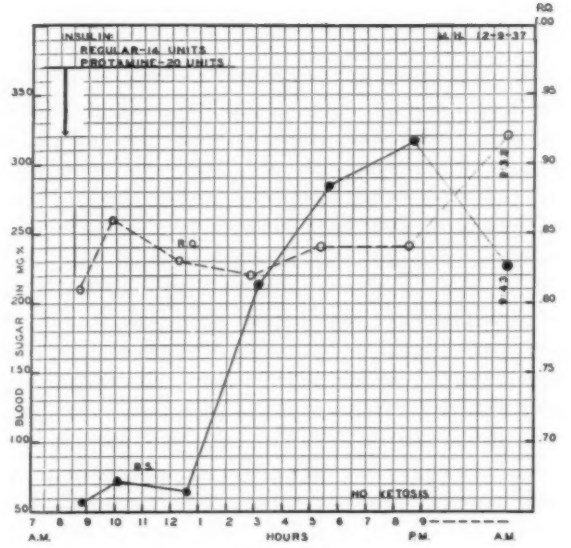

CHART 2A

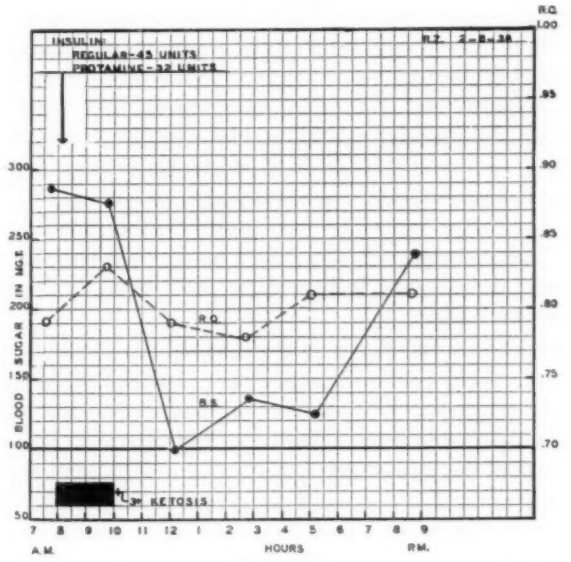

CHART 2B

CHARTS 2A AND 2B. Relative constancy of the respiratory quotients of two diabetic patients in association with wide fluctuations in the blood sugar.

If, however, one attempts to correlate the level of the respiratory quotient with improvement as suggested by a reduction of the blood sugar level during the course of an individual day, difficulties are at once encountered. If insulin acts as a specific stimulus to carbohydrate combustion, one would expect a *lowering* of the blood sugar level to be associated with an increased rate of carbohydrate utilization, *viz.* with a rising R.Q. In Charts 2A (M. H. 12–9–37) and 2B (R. Z. 2–8–38) the respiratory quotient maintains a relatively constant level throughout the day in spite of the wide fluctuations of the blood sugar. Of the thirty individual diabetic days on which observations were made, on only one did the measurements suggest the correlation which would be anticipated if the usual conception of diabetes and insulin action were correct, *i.e.*, if insulin acts as a specific agent to make possible the utilization of carbohydrate materials. One can only conclude that the periodic variations in the blood sugar of diabetic patients do *not* correlate with corresponding changes in carbohydrate combustion as measured by the R.Q.

In the case of two patients, observations were made on the respiratory quotient during periods of insulin reactions with *hypo*glycemia, and on several other occasions during hypoglycemia unaccompanied by clinical symptoms. Instead of rising to 1.0 or thereabouts, the R.Q. remained stationary at a normal level or *decreased* slightly. In no instance was hypoglycemia associated with a rising R.Q. or one that suggested a maximum rate of carbohydrate combustion. Charts 3A (M. H. 11–30–37) and 3B (J. W. 2–11–38) are examples of these results. The abnormal reduction of the blood sugar level accompanying an overdose of insulin is apparently *not* a result of excessive carbohydrate combustion.

Observations on the effects of *too little insulin* on the respiratory quotient were made both during spontaneous swings to hyperglycemia while under treatment and on three occasions when the usual daily dose of insulin was omitted, saline being substituted in its place. In some instances the respiratory quotient remained constant at a normal level; in others it decreased moderately; in no case did it rise appreciably. Charts 4A (J. M. 12–7–37) and 4B (D. L. 4–7–38) illustrate these observations. Thus insufficient insulin with marked hyperglycemia is not necessarily associated with a low respiratory

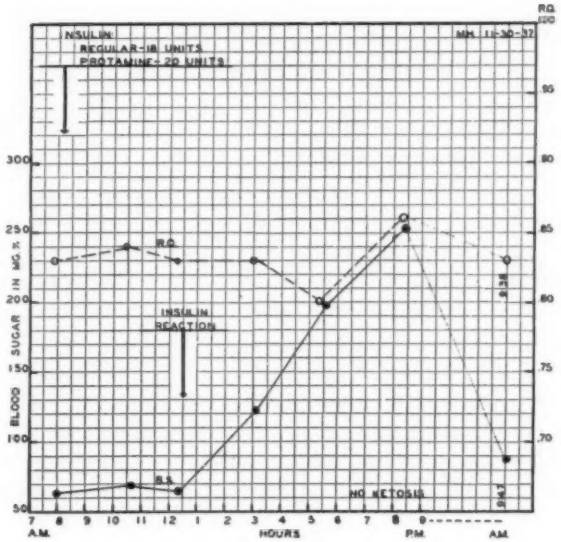

CHART 3A

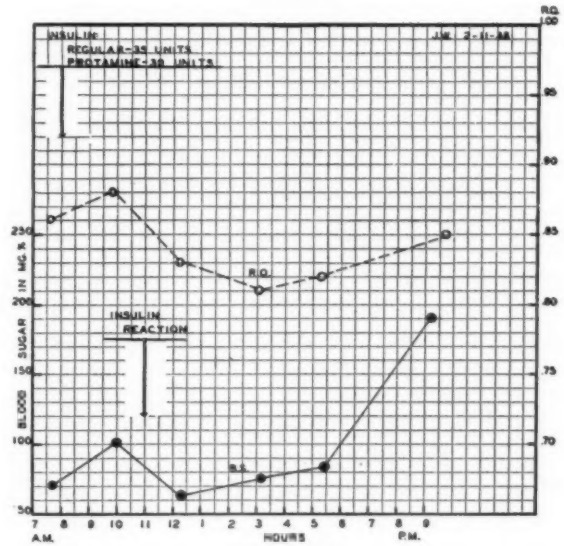

CHART 3B

CHARTS 3A AND 3B. Data obtained in the study of two diabetic patients before and after *hypo*glycemic reactions which occurred during the course of general regulatory therapy. In the former, the respiratory quotient appears unaffected by the low level of the blood sugar; in the latter the R.Q. decreases slightly. In both, the respiratory quotients are in a normal average range.

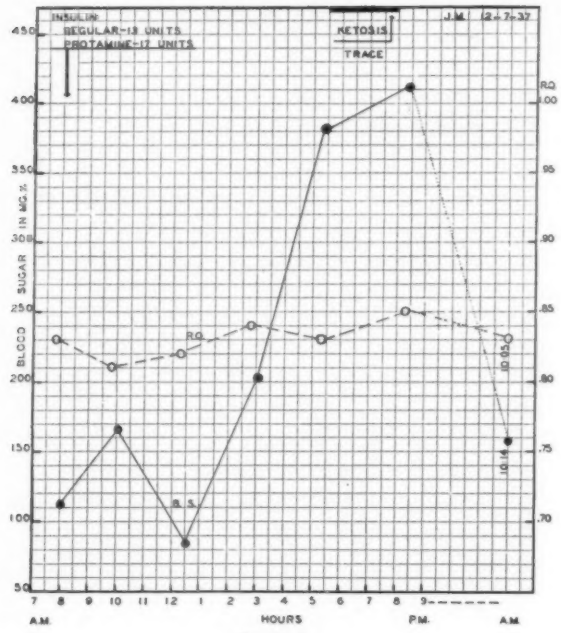

CHART 4A

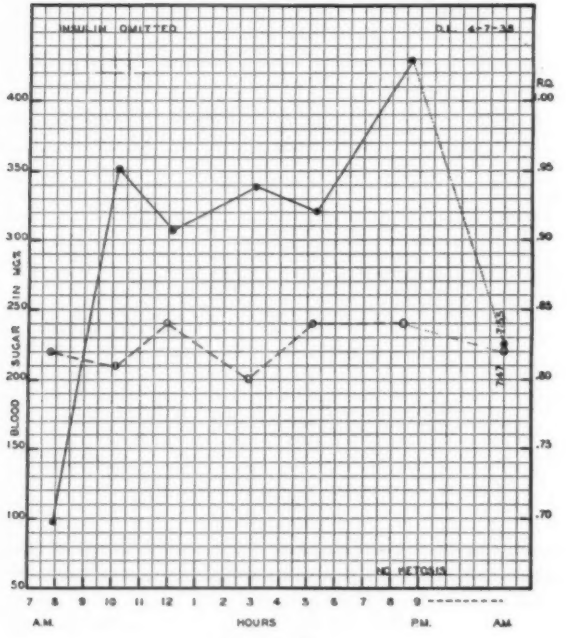

CHART 4B

CHARTS 4A AND 4B. Relation of a sudden marked rise in the blood sugar of two diabetic patients to the respiratory quotient throughout the day. In the former, the *hyper*glycemia occurred during the course of general regulatory treatment; in the latter it was induced by omitting the daily dose of insulin.

quotient level. The effects of insufficient insulin, therefore, are not reflected specifically in an impairment of carbohydrate utilization; in this respect the observations confirm the conclusions reached above, namely, that insulin does *not* specifically affect carbohydrate combustion as measured by the respiratory quotient.

In further confirmation of this, the 178 simultaneous determinations of the blood sugar and respiratory quotient of the diabetic patients were separated into groups representing blood sugars (a) below 100 mg. per 100 cc., (b) 100–200 mg. per 100 cc. (c) 200–300 mg. per 100 cc., and (d) above 300 mg. per 100 cc. The average respiratory quotients were found to be 0.84, 0.83, 0.83, and 0.81 respectively. While this may suggest a slight tendency toward improved combustion when the blood sugar is maintained at a low level, the variations are too small to be of real significance.

Although the carbon dioxide combining power of the blood was not checked routinely during the study, there is no reason to anticipate changes in acid-base equilibrium sufficient to affect the respiratory quotient appreciably. Since such changes are a result of ketosis in diabetes, the results obtained during hypoglycemia, and during hyperglycemia without ketosis, which incidentally comprise most of the observations, can be accepted as reliable. When ketosis developed, the correct respiratory quotient may possibly be 0.02–0.05 lower than the recorded values. However, in a group of patients in whom the CO_2 combining power was checked throughout the day, no significant changes were observed. In no instance were there clinical evidences of acidosis. Such errors would not invalidate the general argument.

These studies which have been described, demonstrate respiratory quotients of diabetic patients which were not anticipated when the work was undertaken. It is true that general improvement in the diabetes was accompanied by an increased level of the R.Q. throughout the day; on the other hand, in any given day, periods of low blood sugar which supposedly represent improvement were *not* associated with a corresponding rise in the respiratory quotient. Blood sugars so low as to induce actual hypoglycemic reactions were unaccompanied by evidences of rapid carbohydrate combustion. Hyperglycemia was observed during periods in which the R.Q. re-

mained stationary at normal levels or decreased moderately. The explanation of these findings is not self evident.

DISCUSSION

The observations which have been presented show clearly that the respiratory quotient of regulated diabetic patients bears no consistent relation to the intensity of the insulin effect as measured by blood sugar. Hypoglycemia may occur while the respiratory quotient is high, average, stationary, or falling. Furthermore, a constant or decreasing R.Q. at a normal or moderately low level may be found during periods in which the blood sugar rises to high diabetic levels; no time relationship was apparent between the respiratory quotient and the swings toward outspoken diabetes. These findings cannot be reconciled with the view that insulin acts as a specific stimulus to carbohydrate combustion.

Such apparent inconsistencies between fact and theory become understandable in the light of recent investigations into the action of insulin on normal animals (3). These experiments showed that in unanesthetized rabbits receiving a constant 6-hour infusion of glucose, the addition of insulin had no significant effect on the respiratory quotient or on the total amount of glycogen deposited in the body. The striking and consistent effect of the insulin was to shift the deposition of glycogen from the liver to the muscles. Since regulated diabetic patients have an essentially normal metabolism of food stuffs, it is reasonable to suppose that an overdose of insulin will act in them as in normal animals, *i.e.*, by shunting the available sugar into the muscles as glycogen. But since the muscle glycogen level and the respiratory quotient of the total animal bear no consistent relation to each other (4), it is not surprising to find insulin hypoglycemia *without* correlated changes in carbohydrate combustion. Insulin hypoglycemia, then, would seem to be a result, not of excessive combustion of carbohydrate, but of an abnormal shunting of the available sugar into glycogen of the muscles where it is no longer in a state for quick mobilization in response to general body needs.

In the present study the respiratory quotient level at the time of hypoglycemia appears at first sight to be independent of all else. Closer study, however, in the light of the relationship demonstrated

recently between R.Q. and *liver* glycogen (4) suggests a reasonable explanation for the foregoing findings. Normally any tendency toward hypoglycemia is quickly adjusted by liberation of glucose from liver glycogen. If the liberation of a large amount of glucose from liver glycogen were necessary to counteract the hypoglycemia, a lowering of the respiratory quotient would be anticipated, as, for example, occurred in the case (J. W. 2–11–38) shown in chart 3B. Such a mechanism, then, leads one to expect a stationary or decreasing level of carbohydrate combustion during insulin hypoglycemia instead of the opposite as would be anticipated from the more commonly held view of insulin action. This explanation, although partly theoretical, agrees with the observations described above, and in view of this agreement, it seems likely that the respiratory quotient of diabetic patients may, as in normal animals (4), signify or correlate with the level of liver glycogen.

The behavior of the respiratory quotient during periods of insufficient insulin finds a possible explanation in a similar way. A comparison of the R.Q. observed in Case I (A. E.) shows that at the time when the diabetes was less well controlled, the level of the R.Q. throughout the day was relatively low; later when general improvement had taken place this level was higher. At first sight this suggests a specific beneficial effect of the insulin on carbohydrate combustion. On the other hand, an equally satisfactory explanation is to be found in an improvement of glycogen reserves. Both animal and human experiments have suggested that differences in the fasting level of the respiratory quotient are associated with corresponding differences in glycogen reserves (4, 5). And in addition to this, the increased level of the respiratory quotient in this patient after treatment which caused him to gain weight is similar to that which has been observed in normal subjects who have either gained weight or have been forced to eat extra amounts of carbohydrate foodstuffs (6). All of this suggests that changes in glycogen reserves may account for the different levels of the respiratory quotient in Case I (A. E.), although, of course, direct observations are impossible.

Insufficient insulin as evidenced by a marked increase in blood sugar either spontaneous or induced by the omission of the daily insulin, was accompanied by a stationary or decreasing respiratory

quotient, often at an average normal level (.80–.84). Carbohydrate combustion did not quickly disappear as would be anticipated if the hyperglycemia were evidence of a lack of the specific agent responsible for this combustion. It seems more likely here also that the R.Q. may be an indication of liver glycogen; a lowering of the R.Q. might then be a reflection of a rapid loss of liver glycogen brought about by insufficient insulin, similar to the relationship shown in (4). The changes in respiratory quotient during insufficient insulin with hyperglycemia, therefore, find an explanation more readily in the effects on glycogen reserves than on tissue utilization.

At present, control of the blood sugar level in diabetes is often considered synonymous with control of the disease itself. Insulin and diet are adjusted with this single criterion in mind. But in the partially regulated patient, as discussed above, hypoglycemia may indicate no more than an excessive deposition of muscle glycogen, and hyperglycemia may develop without changing that more fundamental aspect of carbohydrate physiology, *viz.* combustion. Since therefore neither the intensity of the diabetic process nor the effectiveness of insulin dosage is measurable directly by blood sugar regulation, it is obvious that emphasis may be wrongly placed if the blood sugar level is considered the *sole* criterion of regulation.

What then should be the criteria for judging the regulation of diabetic patients? Theoretically, four aspects of carbohydrate metabolism would seem to deserve attention:

(1) ketosis
(2) respiratory quotient level
(3) conditions affecting the efficiency of insulin action
(4) blood sugar fluctuations

The first of these is obvious to everyone, for ketosis indicates an active diabetic process needing insulin for its alleviation. The second is equally obvious, for without a normal level of the respiratory quotient, the disturbed metabolism cannot be considered corrected. The third aspect, namely, conditions affecting the efficiency of insulin action, is difficult to define specifically at the present time, but appears to involve acid-base balance, state of hydration, level of carbohydrate in the diet, physical exercise, and emotional state. Further study is needed in this direction. The fourth, blood sugar regulation,

is a most valuable aid in recognizing and preventing hypoglycemic reactions, and in evaluating the intensity of the diabetes when urine specimens cannot be obtained. In the presence of a normal respiratory quotient level and efficient insulin action, however, *hyperglycemia* appears to have less significance than has heretofore been attached to it. Glycosuria, while often valuable in a practical way, is subject to the same possible errors as the blood sugar on which it depends. Thus from the physiological point of view, it seems more reasonable to utilize ketonuria, respiratory quotient, and the conditions affecting insulin efficiency as guides in the regulation of diabetic patients than to depend solely on glycosuria or blood sugar level. Clinical experience will, of course, be necessary to establish the relative value of these criteria.

What then is the nature of the disturbance of carbohydrate metabolism in diabetes? Although a definite answer cannot be given, a suggestion which has been offered from time to time in the literature (8) and which appears from the above data and discussion may not be amiss, *i.e.*, that the major aspect of the trouble centers in the liver. The evidence for this theory comes from several sources:

(1) Removal of the liver from diabetic dogs causes a rapid disappearance of the diabetic symptoms.

(2) Insulin appears to influence carbohydrate combustion in diabetes only indirectly. This influence seems to be associated with changes in liver glycogen.

(3) Carbohydrate combustion and respiratory quotient appear to be related to the glycogen content of the liver.

(4) The overproduction of glucose from protein, from glycogen (7), and possibly also from fat in diabetes represents a process which is in many respects the opposite of the inability to form glucose from these same precursors in liver insufficiency.

SUMMARY AND CONCLUSIONS

1. Diabetic patients have been studied in an attempt to correlate insulin action with blood sugar and respiratory quotient.

2. No direct relationship was observed between insulin action and respiratory quotient.

3. Hypoglycemia from overdosage with insulin is not due to an

abnormal rate of carbohydrate combustion. The mechanism, in all probability, consists of an excessive deposition of available glucose as glycogen in the muscles.

4. The blood sugar level by itself does not seem to be an adequate criterion for judging the regulation of diabetes. Other aids are suggested.

REFERENCES

(1) MANN, F. C., AND MCGATH, T. B.: *Arch. Int. Med.* **31:** 797, 1923.
(2) PETERS, J. P., AND VAN SLYKE, D. D.: *Quantitative Clinical Chemistry*, Vol. II, p. 471. Baltimore, 1931.
(3) BRIDGE, E. M.: *Bull. Johns Hopkins Hosp.* **62:** 408, 1938.
(4) BRIDGE, E. M.: *Ibid.* **61:** 349, 1937.
(5) BRIDGE, E. M.: Unpublished.
(6a) BENEDICT, F. G., AND HIGGINS, H. L.: *Am. Jour. Physiol.* **30:** 217, 1912.
(6b) BRIDGE, E. M.: Unpublished.
(7) KOSTERLITZ, H.: *Arch. f. exper. Path. u. Pharmakol.* **173:** 159, 1933.
(8) SOSKIN, S., AND LEVINE, R.: *Am. Jour. Physiol.* **120:** 761, 1937.

BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Shock and Related Capillary Phenomena. By VIRGIL H. MOON. 442 pp. Illus. $3.50. *Oxford University Press, London, New York and Toronto, 1938.*

To the reviewer this volume appears to have two purposes. The first, to stress that there are types of failure of the circulation which are neither cardiac nor vasomotor, but, rather, peripheral vascular (capillary) in origin. The second, that the latter type of failure occurs in a wide range of both surgical and medical disorders.

The best known of these states is traumatic shock but in no way different, nor less important, are the circulatory deficiencies associated with numerous other conditions—hemorrhage, burns, anaphylaxis, and certain forms of intoxication due to poisons, venoms and metabolic disturbances. When the circulation fails in each of these states, the cause is the same: there is damage to widespread capillary areas resulting in capillary atony and increased capillary permeability which in turn produce "an uncompensated disparity between the volume of blood and the volume capacity of the vascular system." This is shock. Whenever and wherever it occurs, there is no essential difference in its manifestations, only variations in its degree of intensity and rapidity of onset.

Repeatedly it is stressed that the fall in the systemic blood pressure is a late and fallacious criterion of the shock state. Often reduced volume of blood flow and reduced blood volume indicate shock while compensatory vasoconstriction still maintains an adequate blood pressure. Hemoconcentration is offered as an early criterion of the development of this state and as an accurate index of its severity. The pathologic picture of shock with its intense minute vessel congestion and edema of certain visceral areas, particularly lung and gastro-intestinal tract, is compared and contrasted with that of passive congestion.

The material is well and clearly presented, the ideas stimulating and the conclusion well based and acceptable. All those who meet shock should find in this book much of value.

L. W. E.

Modern Surgical Technic. By MAX THOREK. 3 vols. 2045 pp. Illus. $35.00. *J. B. Lippincott Co., Philadelphia, 1938.*

Existing treatises covering the field of operative surgery fall, for the most part, into two categories: (1) voluminous systems which are too expensive for many to own and which offer so many and such detailed procedures that they are

confusing to the average student; (2) single volumes which are too abridged to give adequate information and direction.

Dr. Thorek has very successfully supplied a much needed mean to these extremes with three volumes of up-to-date important advances in surgical technic, which include sufficiently detailed descriptions of each procedure in all commonly performed operations. The author belongs to that school of surgeons whose brilliance lies not in seeking to dazzle with manual dexterity or in burning incense to the gods of the gallery, but in satisfying the murmured approval of their own consciences, in saving or prolonging the greatest number of lives, and in restoring their patients to health in the shortest number of days. All who appreciate this surgical attitude will be delighted with the author's handling of the problem in these three splendid volumes.

Having said this, it is fair to criticize certain sections. The discussion of preoperative and postoperative care occupies only 11 pages and is, of course, inadequate. Illustrations for the section on the skull and brain are not nearly so good as those that might have been taken from Dandy's article in Lewis' Practice of Surgery. Dr. Thorek has reproduced drawings from this work in discussing hydrocephalus. On the whole, however, the books are profusely and very well illustrated.

An exposition of the surgical anatomy involved precedes each description of operative procedures. The step-by-step method has been adopted in describing operations, for the benefit of the student or inexpert operator. The only recent publication which approaches this work in value is Horsley and Bigger's *Operative Surgery*.

I. R. T.

Principles and Practice of Obstetrics. By JOSEPH B. DELEE. 7th ed. 1211 pp. Illus. $12.00. *W. B. Saunders Co., Philadelphia, 1938.*

American obstetrics has been fortunate during the past quarter of a century in possessing two distinguished text-books: Williams' *Obstetrics* and DeLee's *Principles and Practice of Obstetrics.* The former, because of its clear and scholarly presentation of underlying principles, has made particular appeal to teachers, investigators and medical students; the latter, by virtue of its emphasis on the minutiae of treatment, has been the favorite reference work of practitioners.

The new edition of DeLee's work represents a thorough revision, scarcely a page remaining unchanged. The sections dealing with the underlying physiology of human reproduction have been augmented and much new material incorporated on endocrinology, menstruation, nidation of the ovum and related topics. These chapters are replete with colored diagrams and illustrations which should prove helpful both to the student and the practitioner.

The most notable advance in clinical obstetrics during the past decade lies probably in the field of analgesia and anaesthesia. These subjects are treated fully, the barbiturates and local anaesthesia receiving especial attention. Sev-

eral modern programs of analgesia are described in detail with full instructions about dosage, dangers and contra-indications. Among other new subject matter is the author's consideration of Caldwell and Moloy's work on pelvic architecture, the Willett forceps in the treatment of placenta previa, and sulphanilamide in puerperal infection.

As usual, the work is distinguished by the large number of beautiful illustrations, two hundred and seventy-one of which are in color. A particularly welcome change is the enlargement of the bibliographies which in previous editions have been inadequate. In summary, this standard work, while keeping unchanged its great storehouse of sound advice on every-day obstetrics, has been brought thoroughly up to date, from both a theoretical and a practical point of view, and should remain pre-eminent in its field.

N. J. E.

Leukemia and Allied Disorders. By CLAUDE E. FORKNER. 333 pp. Illus. $5.00. *The Macmillan Company, New York, 1938.*

As the author states in the preface, the clinical aspects of leukemia, observations on the pathologic physiology of the disease and studies of leukemia and similar diseases in animals, are brought together, for the first time, in a comprehensive monograph. For this purpose about 5000 references have been surveyed and a third of these are cited in the text and are listed with their titles, in the bibliography. The result is the most complete study of the subject which has yet appeared.

The material is well organized and numerous cross references serve to give a picture of the disease as a whole. Wherever possible, statements are supported by evidence as reported in the literature. There are 73 effective illustrations as well as 6 color plates. A few of the latter might be improved. It would also have been desirable to have a more critical evaluation of the literature than the author has seen fit to give. Such criticisms, however, are insignificant in comparison with the usefulness of this book. Dr. Forkner deserves the thanks of the medical profession.

M. M. W.

Human Pathology. By HOWARD T. KARSNER. 5th ed., revised. 1013 pp. Illus. $10.00. *J. B. Lippincott Co., Philadelphia, 1938.*

The fifth edition has been amplified in the light of advances made in the medical sciences during the past three years. Numerous references to recent literature (about 250) have been added, and the voluminous bibliography at the end of each chapter makes this text-book especially useful. Many subjects have been thoroughly revised, such as the etiology of tumor growth, oedema formation, and certain endocrine disturbances; and notable additions have been made to the chapters on diseases of the nervous and cardiovascular systems.

As in past editions, the material is divided into General Pathology and Systemic Pathology. This arrangement, as stated in the first edition, may be useful to the advanced student and to the practitioner. A text-book of pathology, however, is chiefly used by the medical student, and it seems to the reviewer that the frequent repetition which is inevitable in any text divided into General and Systemic Pathology detracts from its usefulness. Without such repetition there would be available space for the description of a good many subjects which are not found in the present edition. For example, the general principles of immunity, certain common deficiency diseases (pellagra, and vitamin A deficiency), several important infectious diseases (the exanthematica, epidemic cerebrospinal fever, undulant, typhus and yellow fever, and malaria), and other diseases could be included.

S. B.

The Prevention of Puerperal Sepsis. By L. COLEBROOK. And *Antisepsis in Midwifery.* By L. COLEBROOK and W. R. MAXTED. 109 pp. Paper bound, $1.00. *Oxford University Press, New York and London, 1938.* (Oxford Medical Publications.)

This booklet consists of a summary of the researches by Colebrook and his associates at the Queen Charlotte's Hospital, in the field of puerperal infection. There are two parts, the first dealing with the prevention of puerperal sepsis, and the second with antisepsis in midwifery.

In the first section the author discusses the etiological importance of the hemolytic streptococcus, especially in regard to serological grouping, and then considers measures for the prevention of puerperal infection by this organism.

The section on antisepsis deals with investigations of the efficacy of certain antiseptics against the staphylococcus and streptococcus pyogenes. The value of "Dettol," a British proprietary antiseptic, is extolled.

J. F. S., JR.

Synopsis of Genitourinary Diseases. By AUSTIN I. DODSON. 2nd ed. 294 pp. Illus. $3.00. C. V. Mosby Company, St. Louis, 1937.

Dr. Dodson, in his preface to the first edition, states that "The purpose of this book is to present a synopsis of genitourinary diseases so that the essential facts connected with urology may be readily grasped by the student of medicine and serve as a handy reference for the physician in practice."

The author has been eminently successful in achieving this purpose. The first chapter is devoted to urologic diagnosis and is followed by a second chapter on instruments and minor urologic procedures. No attempt is made to present the field of cystoscopic examination and ureter catheterization, as the author rightly feels that these more technical procedures should not be included in a work of this character.

A short, but comprehensive, chapter on anatomy of the uro-genital tract then follows. The diseases of the genitourinary tract are then taken up in the most logical manner from the student's standpoint, by discussing them under the headings of congenital anomalies, non-tuberculous infections, tuberculosis, injuries, calculous disease, neurogenic dysfunctions and tumors. These subjects are well presented in a brief systematic way with references to text books or the literature so that one interested in a particular subject may readily find the authoritative sources. The lists, with sample meals, to produce an acid ash, high vitamine, or ketogenic diet should be of special value to general practitioners.

It is unfortunate that the publication of this edition occurred in 1937, at a time when our knowledge of the great value of mandelic acid and sulfanilamide was being established on a firm basis, so that the author gives little space to the discussion of these newest and most powerful agents against renal infection. In his discussion of infections of the genitalia, there is a serious omission, in that no mention is made of lymphogranuloma inguinale. The other subjects are considered adequately, so that the book certainly serves its purpose as a review compendium of diseases of the genitourinary tract for the medical student and will also offer to the general practitioner a convenient synopsis from which he may review the simpler methods of diagnosis of any urological problem which may present itself to him in his practice and the book will also present to him, in an intelligent manner, the various therapeutic methods which can be employed by the specialist in urology, and what results may be expected from them.

J. A. C. C.